بسمـــ الله الرحمن الرحيمـــ

فريق عمل كل الطب

يُقدمـــ

سلسلة كتب د/أحمد موافي

In Capsule Series

تم الرفع بواسطة فريق عمل كل الطب

ALLTEB MEDICAL TEAM

مجمع ومنقول من أكثر من مصدر

جزى الله خيرا كل من ساهم في هذا العمل

لا تنسونا من صالح دعائكمـــ،،

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LIVER

Introduction:

- Liver is the largest & heaviest internal organ in the body (1500 gm).
- The liver is the **main industrial centre** of the body it's involved with almost all

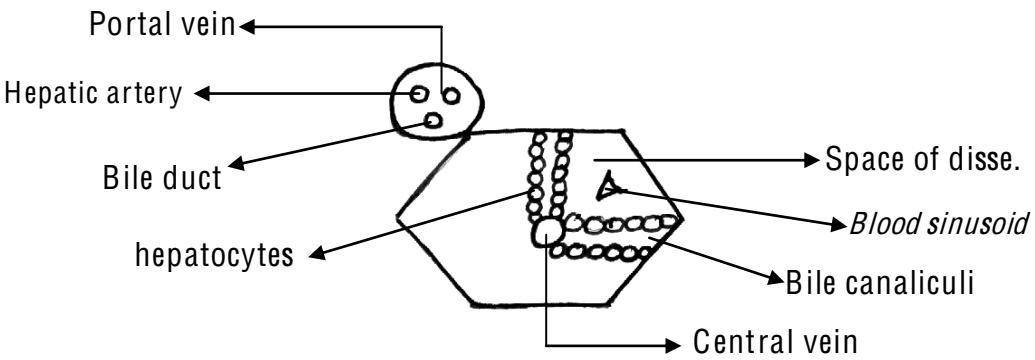
  the biochemical pathways that allow growth, supply nutrients, provide energy & aid reproduction.
- Liver cells (*hepatocytes*) go thousands of complex biochemical reactions every second in order to perform these function.
- In brief, *you can't **live** without **liver**.*

Anatomy:

- The liver is located behind the lower ribs, right below diaphragm on the right side of abdomen separated superiorly by falciform ligament & inferiorly by ligamentum teres.
- Right lobe is much larger & has 2 additional lobes (*caudate & quadrate*)

Histology:

- **Hepatic lobule:** is the basic unit for liver function:



- The walls of the sinusoids consist of endothelial & macrophage cells known as "*Kupffer cells* "
- These kupffer cells phagocytes bacteria, viruses & immune complexes.

Blood Supply of the liver : 25% of the resting cardiac output

– Liver has double blood Supply :

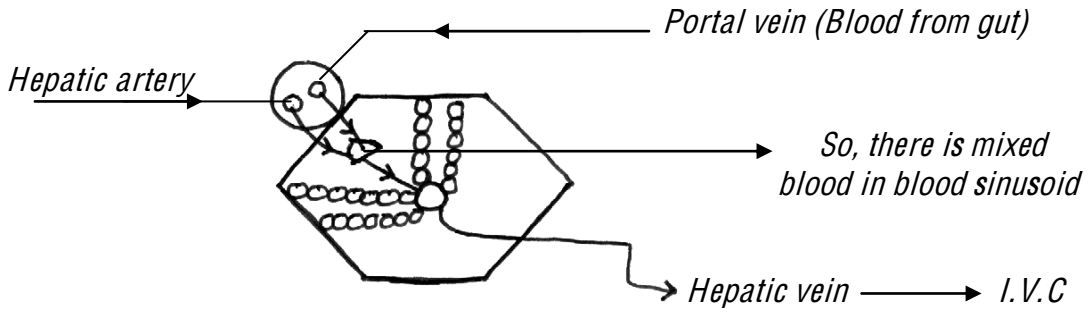
i- Hepatic artery (1/3) → carries oxygenated blood.

ii- Portal vein (2/3) → brining blood from the intestine & spleen.

Venous drainage:

Drainage is via the hepatic veins into the inferior vena cava.

Portal circulation:



Liver functions : (Details : see liver function tests)

i. Liver is very important in proper protein, carbohydrate & fat metabolism.
ii. Making bile.
iii. Detoxification: filtering of the blood.

You can spend a lifetime studying the liver and still not understand all of its physiology!!

- The liver has great reserve power, it can loss ¾ of its cells before it stops functioning.
- Liver cells can regenerate themselves, this regenerative ability allows ɑ diseased liver to return to normal function in some cases. Very few organs in the body have this ability.
- So, this great reserve power means that diseases that affect the liver show no symptoms in early stages & this makes the prognosis worse.

Rule of 6 in Hepatology : ☺

1. Pathogenesis (Etiology) of Ascites in hepatic patient …… 6 items.
2. Treatment of Ascites in hepatic patient. …….. 6 items
3. Precipitating factors of hepatic encephalopathy…….. 6 items.
4. c/p of hepatic encephalopathy (pre coma)……..6 items.
5. Treatment of hepatic encephalopathy…….. 6 items.
6. c/p of portal hypertension …….. 6 items
7. Complications of portal hypertension…….. 6 items.
8. Investigations of portal hypertension…….. 6 items.
9. Treatment of portal hypertension (esophageal varices)…… 6 items.
10. Prevention of esophageal varices…… 6 items.
11. Complications of hepatitis …….. 6 items.
12. Investigations of hepatitis…….. 6 items.
13. Treatment of acute hepatitis …… 6 items.
14. Indications of liver transplantation …….. 6 items.
15. Complications of liver transplantation …….. 6 items.
16. Causes of hepatomegally …… 6 items.

All that you need in hepatology is just to remember & enumerate these items (6 x 16 = 96 items) , Try to recall these 96 items every night.

Liver function tests

I – Plasma proteins:

- Total proteins : 6 – 8 gm %
- Albumin : 4 – 5 gm % (Totally formed in the liver)
- Globulins : 2 – 3 gm % (α , B in the liver, δ in RES)
- Albumin : globulin (A : G ratio) = 2 : 1

- The liver is the principle site of synthesis of all circulating proteins EXCEPT δ globulins (immunoglobulins), which are produced in the reticuloendothelial system (RES)
- It synthesizes all coagulation factors EXCEPT factor VIII.
- Amino acids are degraded by transamination & oxidative deamination to produce ammonia, which is then converted to urea by the liver and excreted by the kidneys.

In chronic liver disease:

- ↓ Albumin, ↑ globulins (to maintain normal total plasma proteins)
- ↓ A/G ratio & may be **reversed**.
- Albumin is NOT affected in acute liver diseases.

δ globulins increase in liver diseases due to stimulation of antibody against :

- Antigen released from damaged liver cells.
- Antigens absorbed from gut & not cleared by the diseased liver.
- Viral antigen.

Ask for immuno-electrophoresis to know the type of Ig ***MCQ***

- IgG : chronic active hepatitis.
- Ig**A** : **A**lcoholic liver disease.
- IgM : 1ry biliary cirrhosis.

II – Fat metabolism : (Cholesterol : 150 – 250 mg %)

- Normally cholesterol is esterfied in liver & excreted in bile, So :
- **In obstructive Jaundice:** ↑↑ cholesterol with normal esterfication.
- **In liver cell failure:** normal level of cholesterol with ↓↓ esterfication.

N.B. *Hepatatocytes have a great power for excretion of cholesterol so, it is normal even in LCF.*

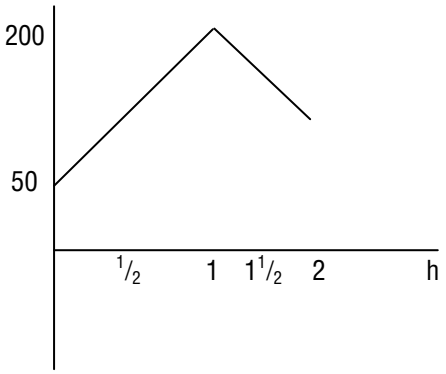
III- Carbohydrate metabolism :

Role of liver in CHO metabolism: (Carbohydrate buffer)

- During fasting : ↑ glucogenolysis & gluconeogenesis → ↑ glucose level.
- After feeding : ↑ glucogenesis → ↓↓ glucose level.
- In prolonged starvation : ketone bodies & fatty acids are used as alternative sources of fuel and the body tissues adapt to a lower glucose requirement.

Blood sugar curve : Lag sugar curve

- During fasting : hypoglycemia.
- After feeding : ↑ glucose level (> 180 mg % so may appear in urine)



DD of lag sugar curve:

- Chronic liver disease.
- Hyperthyroidism.
- After gasterectomy.

IV- Bilirubin : *see jaundice*

- Total serum bilirubin : (N : 1 mg %) : It ↑ in all types of jaundice.
- Unconjugated bilirubin:
  - Normally > 80% of total bilirubin. (0.8 mg%)
  - ↑ in hemolytic jaundice & hepatocellular jaundice.
- Conjugated bilirubin:
  - Normally < 20% of total bilirubin. (0.2 mg%)
  - ↑ in obstructive jaundice & hepatocellular jaundice.

- Bilirubin in urine:
  - Normally there is no bilirubin in urine.
  - Bilirubin is present in urine in obstructive & hepatocellular jaundice.
- Urobiolinogen in urine: (colorless)
  - ↑ in hemolytic & hepatocellular jaundice.
  - ↓ in obstructive jaundice.
- Stercobilinogen in stool:
  - ↑ in hemolytic jaundice.
  - ↓ in obstructive & hepatocellular jaundice.
- Bile salts : Appear in urine in obstructive jaundice → frothy urine.

V- Enzymes :

1- Transaminases :

- **Aspartate aminotransferase** :
  (AST, **S**erum **g**lutamic **o**xalocetic **t**ransaminase, SGOT) : 8 – 40 u/l
- **Alanine aminotransferase**
  (ALT, **S**erum **g**lutamic **p**yruvic **t**ransminase, SGPT) : 5-30 u/l
- These enzymes present within hepatocytes & released in liver diseases e.g. acute hepatitis :↑ (up to 20 fold) -chronic active hepatitis :↑ (3-5 fold)
- SG**P**T is more s**P**ecific for liver diseases than SGOT.
- SGOT may increase also in myocardial infarction & muscle injury.

2- Alkaline phosphatase (ALP) :

3-13 king Armstrong units or 40 – 180 u/l.

- This is present in liver, bone, intestine & placenta.
- Moderate ↑↑ (13 – 30 KAU) : in hepatic failure.
- Marked ↑↑ (> 30 KAU) :

Obstructive Jaundice, Space occupying lesions, bone disease.

3- δ glutamyl transpeptidase (δGT) & 5-nucleotidase:

- To decide that the high level of ALP is due to liver disease & not bone disease.
- If the ALP is normal, a raised serum δGT is a good guide to alcohol intake.

VI- Prothrombin time (PT): *Normally 12 : 14 seconds.*

- **It is prolonged in:**
  - Acute & chronic liver cell failure : it's due to short half life of Coagulation factors.
  - Obstructive Jaundice : due to vitamin K deficiency.
- **Importance of PT:**
  - ➲ To assess the severity & prognosis of liver diseases.
  - ➲ Follow up in patient under anticoagulant.
  - ➲ Before any invasive technique e.g. liver biopsy.

VII – Alpha fetoprotein: Normally it is < 20 ng / ml.

- Marked elevation (> 2000 ng / ml): highly suggestive for hepatoma.
- Mild or moderate elevation:
  - º Cirrhosis.
  - º Hepatitis.
  - º Pancreatitis.
  - º GIT tumor.

- *Normal levels of α fetoprotein do not*

VIII- Bromosulphalein test (BSP):

For detoxifying function of the liver not performed now because of its side effects.

Immunological tests :

- ✓ Antimitochondrial antibody (AMA) : 1ry biliary cirrhosis (95%)
- ✓ Anti- nuclear & anti-smooth muscle antibodies : autoimmune hepatitis.
- ✓ Antinuclear cytoplasmic antibodies : primary sclerosing cholangitis.

LIVER CIRRHOSIS

Definition :

Cirrhosis is defined as **fibrosis** & **nodular regeneration** resulting from **hepatic injury**, ending in **loss of normal liver architecture.**

Pathogenesis:

i- The main damage in cirrhosis is triggered by scaring (fibrosis) that occurs from repeated injuries due to alcohol, viruses,……..

ii- In response to the scaring, liver cells regenerate in abnormal pattern & form nodules around the scar → irreversible loss of architecture.

iii- The scar tissue & regenerated nodules block the flow of blood and bile through the liver, preventing it from working as it should.

Etiology:

1- **A**lcoholic cirrhosis (Laennec's cirrhosis).
2- **B**iliary cirrhosis.
3- **B**ilharziasis ?
4- **C**hronic hepatitis (**Post hepatitis cirrhosis**).
5- **C**ardiac cirrhosis.
6- **C**ryptogenic (Idiopathic) cirrhosis.
7- **D**rugs : **M**ethotrexate , **I**NH , **M**ethyldopa , **A**miodarone.
8- **M**etabolic :
   - Hemochromatosis. (↑ Fe)
   - Hepatolenticular degeneration. (↑ Cu)
9- **M**iscellaneous :
   - Severe malnutrition.
   - α_1 antitrypsin deficiency.

Classification of cirrhosis:

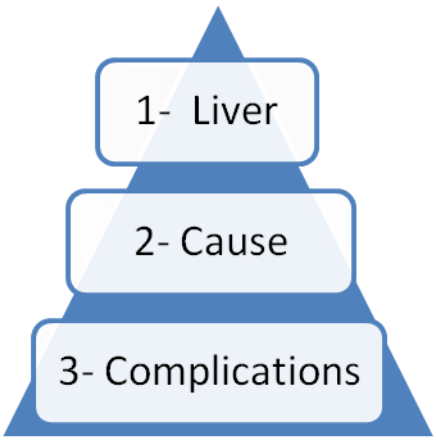
i. Etiological classification.
ii. Morphological classification: Micronodular , Macronodular , Mixed.
iii. Functional classification : Compensated & decompensated cirrhosis.
iv. Child's classification : to assess the severity of liver cirrhosis.

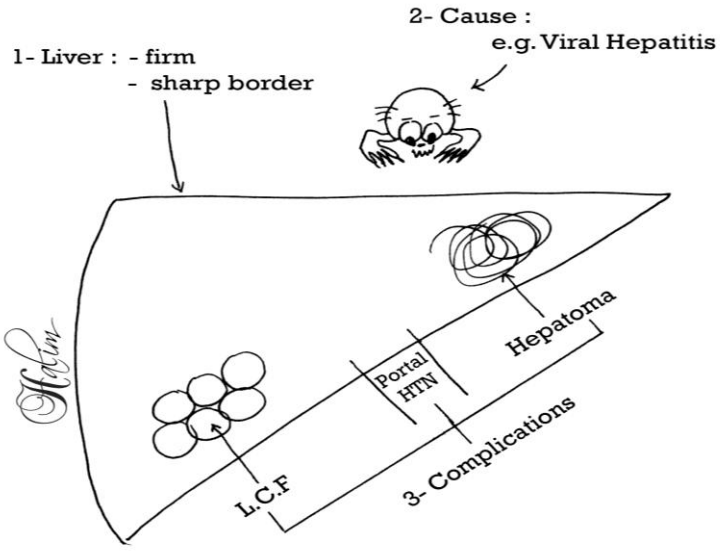
Clinical picture:

a- **Compensated cirrhosis** (*Asymptomatic*) : No LCF or portal hypertension

Many patients with liver cirrhosis are asymptomatic for years.

b- **Decompensated cirrhosis** (*Manifest cirrhosis*) :





i. **Liver :**

- **Firm & Sharp border** .
- Shrunken. (*the liver may be enlarged in early cases but with progression of the disease ,it shrinks*)

ii. **Clinical picture of the cause e.g.**

- Post hepatitis: history of hepatitis …
- Alcoholic cirrhosis : history of chronic alcohol intake.
- Hemochromatosis: Bronzed DM….

iii. **Clinical picture of the complications :**

- Liver cell failure : ..... see later.
- Portal hypertension : ..... see later
- Hepatoma may occur : ..... see later

Investigation:

i- Investigations for the cause e.g. for hepatitis.

ii- Investigations for the liver :

- Liver imaging : ultrasound , CT.
- Liver biopsy is the surest diagnosis.

iii- Investigations for the complications :

- Investigations for liver cell failure (*Liver function tests*).
- Investigations for portal hypertension.
- Investigation for hepatoma : Tumor marker (α-feto protein, carboxy prothrombin)

Child- Turcotte Paugh score : *to assess the severity of liver cirrhosis*

	1 point	2 points	3 points
Encephalopathy	None	Mild (grade 1-2)	Marked (grade 3-4)
Ascites	None	Mild	Marked
Serum albumin (gm%)	> 3.5	3 - 3.5	< 3
Serum bilirubin (mg%)	< 2	2 - 3	> 3
INR (International normalized tissue)	< 1.7	1.7 - 2.3	> 2.3

A patient is considered to be :

- ➲ Child class A : < 7 points
- ➲ Child class B : 7-9 points
- ➲ Child class C : > 10 points.

Treatment:

Liver damage from cirrhosis can't be reversed, but treatment can stop or delay further progression and reduce complications.

i- Treatment of the cause e.g. interferon for viral hepatitis.

ii- Treatment of liver cell failure.

iii- Treatment of portal hypertension.

iv- Drugs to decrease liver fibrosis (*Antifibrotic*) : still under trial

- Colchecine → ↑ collagen destruction.
- Penicillamine → ↓ collagen synthesis.

v- **Hepatic transplantation** is the best hope but many patients are not suitable.

Alcoholic Cirrhosis

Etiology: Alcoholic cirrhosis usually develops after more than 10 years of heavy drinking

1- Alcohol → ↓ appetite & malabsorption → nutritional cirrhosis.

2- $Alcohol \xrightarrow[dehydrogenase]{Alcohol} H^+ + Acetaldhyde \underset{Direct\ Hepatotoxic}{\downarrow}$

Pathology:

- **M**icronodular cirrhosis.
- **M**allory bodies: esinophilic deposits.

Clinical picture:

1- **General C/P of cirrhosis**. (LCF > pH)

2- C/P of the cause : History of prolonged alcohol intake>10years *(Alcoholism)*

Features of chronic alcoholism:

- GIT : Gastritis, hepatitis, pancreatitis, malabsorption.
- CNS: Tremors , Amnesia (*Korsakow's syndrome*), headache & migraine.
- Cardiac : cardiomyopathy.
- Blood: hemolytic anemia.
- Immune: recurrent infection.
- Metabolic: Hypoglycemia, hyperlipidemia.
- Bilateral parotid enlargement.

Investigation: general investigations for cirrhosis.

Treatment:

- Stop alcohol intake.
- General measures for cirrhosis.
- Essential amino acids.
- **C**olchecine , **C**ortisone.

N.B. <u>Alcoholic liver diseases:</u>

1- Fatty liver (*reversible*) :

Alcohol → ↑ fat entry to hepatocytes.

→ ↓ fat secretion from hepatocytes.

2- <u>A</u>lcoholic hepatitis : mimic viral hepatitis

- ↑↑ Ig**<u>A</u>**
- If ratio of SGOT: SGPT > 2:1 → suggests alcohol hepatitis.

3- Cirrhosis (LCF > PH)

Post hepatitis Cirrhosis

Etiology: following virus B , C & D.

Pathology:

- Pathology of cirrhosis itself.
- Ground glass appearance.
- +ve orcien stain
- Features of chronic active hepatitis.

Clinical picture:

- Clinical picture of cirrhosis.
- Past history of virus hepatitis. (see later)

Investigation:

- Investigation for cirrhosis.
- Detection of hepatitis markers.

Treatment:

- General measures for cirrhosis.
- Treatment of chronic active hepatitis.
- Hepatitis B vaccine for prevention.

Bilharziasis

(**pH** > LCF) details : see later

- Bilharziasis causes portal hypertension & periportal fibrosis but not cirrhosis.

  Indeed, liver function remains remarkably good in chronic infection.

- Cirrhosis with marked fibrosis may occur by 2 mechanisms :

  1- Combined etiology with virus C.

  2- Ag- Ab complex.

Cardiac Cirrhosis

Etiology: *Due to long standing liver congestion* (Rare & Late)

1- RSHF

2- Tricuspid valve disease.

3- Constrictive percarditis & pericardial effusion

4- Inferior vena cava obstruction.

5- Budd - Chiari syndrome (obstruction of the large hepatic veins)

6- Veno-occlusive disease. (obstruction of the small intrahepatic veins).

Clinical picture: Again: cardiac cirrhosis is rare & late.

- General features of cirrhosis. (Portal hypertension occurs before liver cell failure)
- Liver is enlarged, tender , soft then firm with sharp border.

Investigation:

- The same as cirrhosis.
- Investigation for the cause e.g. echocardiography.

Treatment:

- General measures for cirrhosis.
- Treatment of the causes e.g. heart failure.

Budd–Chiari syndrome

Definition :

It's obstruction of large hepatic veins due to :

- Thrombosis e.g. Polycythemia rubra vera, OCP, PNH, Behcet syndrome, Atrial myxoma, Antiphospholipid syndrome.
- Obstruction (*tumor*).
- Idiopathic.

All of the following may be etiology of Budd-Chiari syndrome EXCEPT :
a) Congenital hepatic fibrosis.
b) Antiphospholipid syndrome.
c) Oral contraceptive pills.
d) Right atrial myxoma.

C / P :

- Acute stage :
  - Triad of : Abdominal Pain, Ascites , **Rapidly enlarged** tender liver.
  - Manifestations of fulminant hepatic failure may occur.
- Chronic stage: features of cardiac cirrhosis.

Edema LL & dilated veins over the abdominal wall & back suggest IVC obstruction.

Investigations :

1) Laboratory :
   - Elevated liver enzymes & bilirubin.
   - Assessment of hypercoagulability state.
2) **Imaging** :
   - Duplex ultrasound.
   - CT & MRI of the abdomen.
   - Hepatic venography : diagnostic but invasive.
3) Liver biopsy.

Treatment :

- Long term anticoagulant in a chronic cases.
- Thrombolytic therapy in acute cases.
- Surgical shunt or TIPS (**T**ransjugular **I**ntrahepatic **P**ortosystemic **S**hunt) : to divert blood flow around the obstruction.
- Needless to say plus : general treatment of cirrhosis e.g.
  - Control of ascites & hepatocellular failure.
  - Liver transplant : is an effective treatment for Budd-Chiari. It is generally reserved for patients with fulminant hepatic failure.

Biliary Cirrhosis

- It's cirrhosis caused by prolonged biliary obstruction.
- Bile is very irritant to the hepatocytes if retained.

(A) Primary biliary cirrhosis:

Autoimmune disease leading to destruction of intra-hepatic bile duct.

Clinical picture : ♀ 30-50 Y

- Asymptomatic (⅓)
- Fatigue (most common).
- Itching occurs months before jaundice because retention of bile salts can occur before significant retention of bilirubin. (the cause of itching is still questionable)
- Obstructive Jaundice.
- Clubbing.
- Hepatomegaly.
- Malabsorption of fat - soluble vitamins (A , D , E , K) :
    - Vit D → Osteomalacia.
    - Vit K → Bleeding tendency.
- Associated immune disorders : SLE, 30% of patients have thyroid disorders.
- Xanthelasma 2ry to hypercholesterolemia.
- Complications of cirrhosis e.g. LCF, Portal hypertension.

Medical causes of itching:

- 1ry biliary cirrhosis.
- Obstructive Jaundice.
- DM
- CRF
- Hemolytic anemia.
- Polycythemia.
- Lymphoma.
- Leukemia.

Investigation:

i. Serology : It's an autoimmune disorder so, there are : MCQ
   - **Anti-mitochondrial antibody (AMA)** : +ve in 95%
   - ↑ IgM.

ii. Liver function test : obstructive jaundice (↑ Alkaline phosphatase , ↑ direct bilirubin)

iii. Liver imaging : US , CT → enlarged liver with no dilated intra-hepatic biliary radicals.

iv. Liver biopsy is diagnostic.

Treatment:

- Immunosuppressive: Pencillamine, Azathioprine.
- Symptomatic treatment : e.g. Cholestyramine for itching.
- ***Cortisone is contraindicated*** as it increases osteomalacia and osteoprosis.

B) Secondary biliary Cirrhosis:

i. **Extrahepatic** : stone, stricture.

   N.B. Cancer head of pancreases usually of short duration so cirrhosis usually doesn't occur.

ii. **Intrahepatic**: See obstructive Jaundice.

- Clinical picture , investigations & treatment : of obstructive jaundice. see later

How to differentiate between extrahepatic & intrahepati biliary obstruction?

1- US :

- Intrahepatic ⟶ constriction of intrahepatic bile radicals.
- Extrahepatic biliary obstruction → dilation of intrahepatic bile radicals.

2- Cortisone test.

3- Clinical differentiation : " see jaundice "

Hemochromatosis *"bronzed diabetes"*

Definition: (autosomal recessive disorder) The responsible gene is : HFE gene on **chromosome 6**

It's a hereditary disease characterized by excessive absorption of iron resulting in ↑ of total body iron with its deposition in several organs.

Etiology:

- Excessive iron absorption due to absence of mucosal block (autosomal recessive)
- Here, body iron reaches up to 60 gm (N : 3-4 gm)

Clinical Picture:

More common in ♂ (no menstruation)

1- **Liver** : liver cirrhosis (with an increased risk of hepatoma 20%)
2- **Heart** : Cardiomyopathy , arrhythmias.
3- **Skin** : Bronzed color due to stimulation of melanocyte.
4- **Pancreas** : Diabetes mellitus.
5- **Mental** disturbance.
6- **Testicular** atrophy.
7- **Adrenal gland :** adrenal failure.
8- **Arthritis.**

Investigation:

i. **L**aboratory :
   - Serum ferritin & transferrin : ↑
   - Total iron binding capacity (TIBC) : ↓

ii. **L**iver imaging : abdominal CT & MRI.

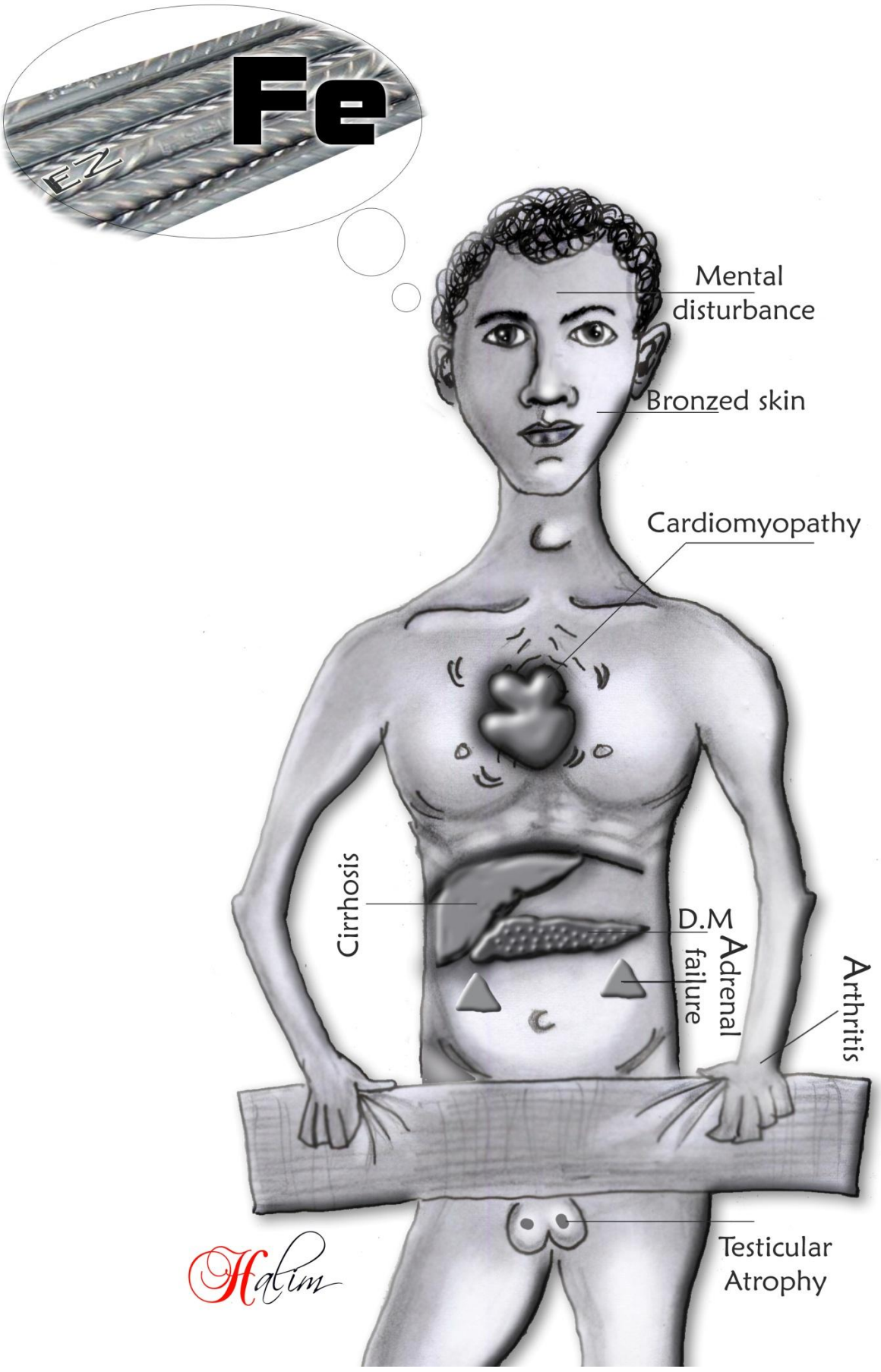
iii. **L**iver biopsy.

Treatment:

i. Treatment of the cause :
   - Repeated venesection: once/week (every bag of blood (500ml) contains 250 mg iron)
   - Iron chelator: Desferal

ii. Symptomatic treatment : DM , Cardiomyopathy, …..

iii. Treatment of cirrhosis : liver transplant for end stage liver disease.



Hemochromatosis

Hepatolenticular Degeneration "*Wilson's disease*"

Etiology: (autosomal recessive disorder) The responsible defective gene is : ATP 7B on **chromosome 13**.

In Wilson's disease copper absorption is normal but there is a deficiency in hepatic formation of "Ceruloplasmin" which is the principal transport protein for copper & necessary for biliary excretion → so free copper will be released to the blood → Abnormal deposition of Cu in several organs (liver , brain , eye) & urinary excretion of copper is increased.

Clinical picture:

- **Liver** : hepatitis (self limited) , may progress to cirrhosis.
- **Lentiform nucleus** (Basal ganglia) → extrapyramidal manifestation e.g. tremors.
- **Kidney** → renal tubule damage which lead to albuminuria & aminoaciduria.
- **Eye** → Kayser – Fleischer ring (green brown ring around the edge of the iris)

Investigation:

- ↓ ceruloplasmin level.
- ↓ blood copper level.
- Liver biopsy.

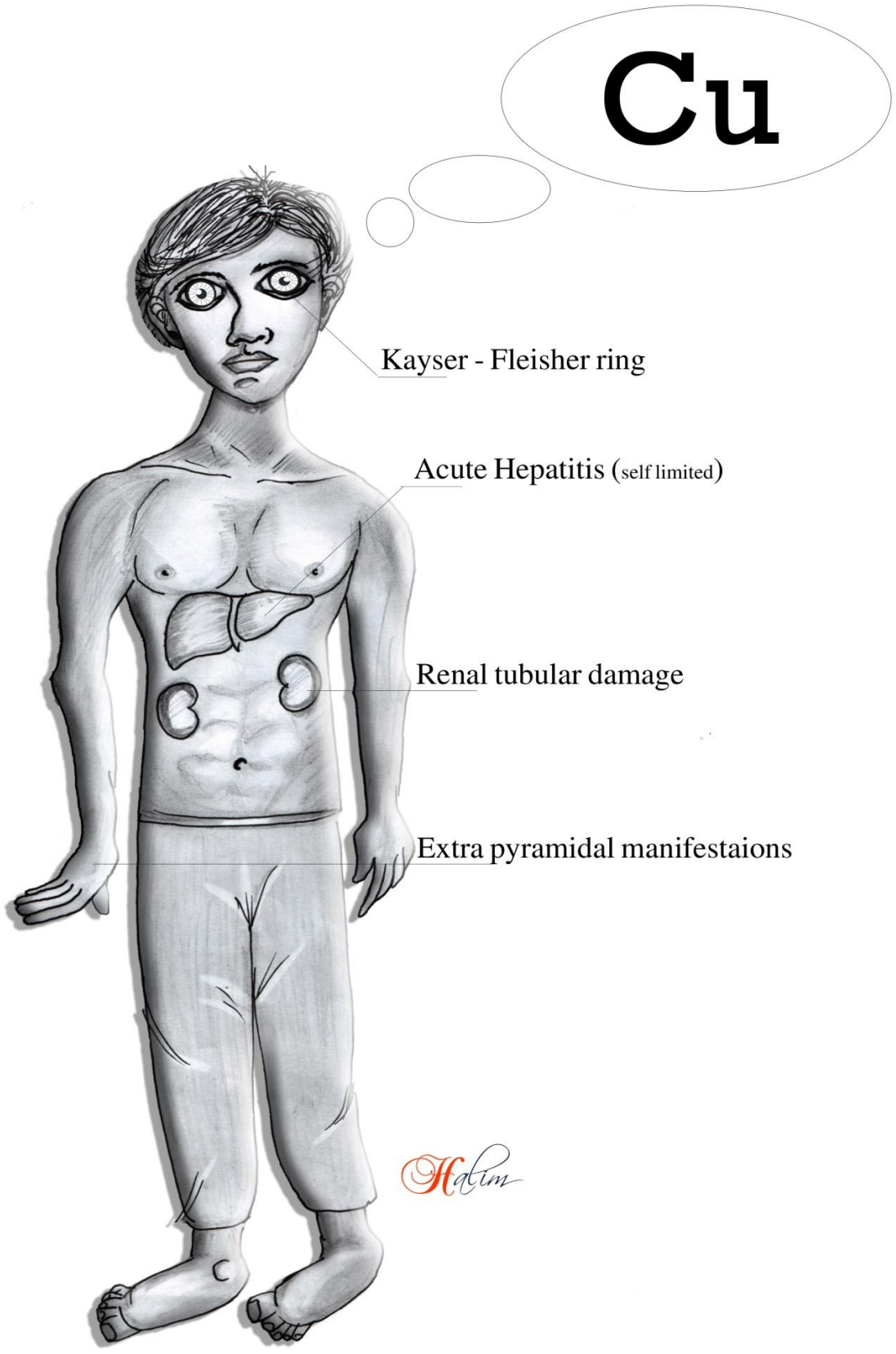
- **The question now is : who should be screened for Wilson disease ?**
- Anyone with unexplained liver disease or neurological symptoms with evidence of liver disease.

Treatment:

i. Treatment of the cause :
   - Penicillamine or trientine hydrochloride : increase urinary excretion of Cu
   - Zink acetate : blocks the absorption of copper.
   - Restriction of copper in diet : ↓ liver , mushrooms.

ii. symptomatic treatment.

iii. Treatment of cirrhosis : liver transplant.



Wilson's disease

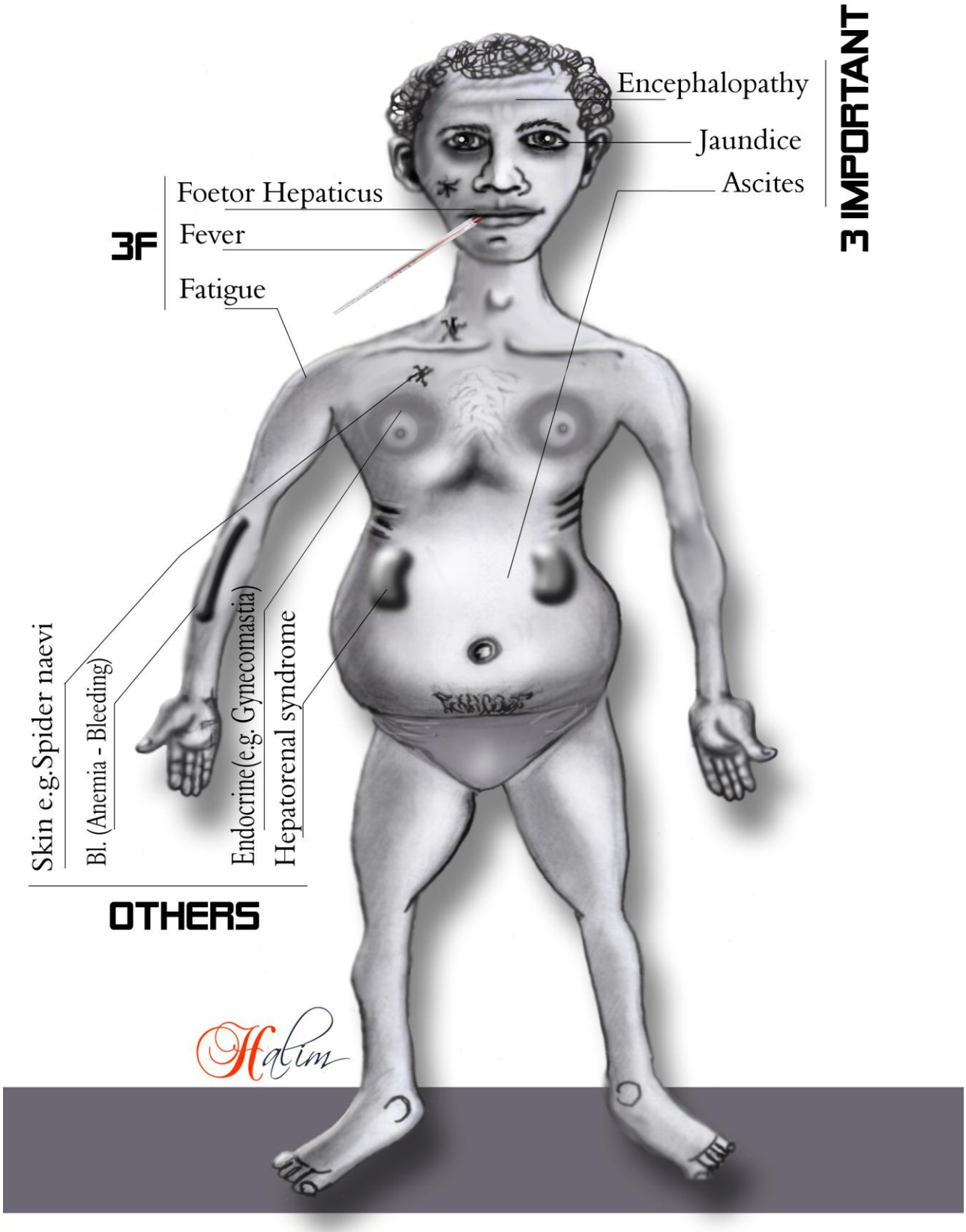
LIVER CELL FAILURE

Etiology :

1. Infections: viral hepatitis. B, C, D
2. Chemicals :
    - Alcohol .
    - **D**DT, **H**alothan, **P**aracetamol , **I**NH
3. Physical: Severe burns & hyperthermia.
4. Terminal stage of :
    - Liver cirrhosis.
    - obstructive jaundice
    - chronic hepatitis.
    - malignancy

Clinical Picture of liver cell failure:

1. **F**atigue, anorexia, loss of weight
2. **F**ever.
3. **F**etor hepaticus.
4. **Jaundice**
5. **Ascites**
6. **Encephalopathy**
7. Skin manifestations.
8. Endocrinal manifestations. (Hormonal)
9. Cardiovascular manifestations.
10. Hematological manifestations.
11. Hepatorenal syndrome.


3 IMPORTANT
Encephalopathy
Jaundice
Ascites
3F
Foetor Hepaticus
Fever
Fatigue
OTHERS
Skin e.g.Spider naevi
Bl. (Anemia - Bleeding)
Endocrine(e.g. Gynecomastia)
Hepatorenal syndrome
Halim

I. **Fatigue, anorexia & loss of weight.**

II. **Fever:** (low grade & prolonged) due to :

1) Necrosis of liver cells → release of pyrogens → stimulation of heat regulating center.
2) Bacteremia due to failure of the liver to clear bacteria from the circulation.
3) Bacteria bypass the liver through porto-systemic shunts reaching the systemic circulation.

III. **Fetor hepaticus:**

- It's musty, pungent breath odor ↑ by constipation & ↓ by defecation.
- It's due to failure of hepatic detoxification of mercaptans (which is normally absorbed from intestine) due to liver failure or shunts. → excreted in mouth with breath.

IV. **Jaundice:** Failure of liver to deal with bilirubin (*see later*)

V. **Ascites:**

Ascites may develop gradually as a result of gradual deterioration of liver functions or acutely e.g. GI hemorrhage, sepsis, or hepatocellular carcinoma.

Pathogenesis : **6 Items**

1. **Hypoalbuminaemia** (< 3gm%) : *The most important factor*.

   Due to diminished synthesis of albumin by the liver.

   NB : *Patient with liver cirrhosis & ascites with normal albumin → suspect other causes of ascites e.g. TB peritonitis.*

2. **Portal hypertension:**

   This factor alone rarely produce ascites, it acts as just a localizing factor (It localizes the transudate to the peritoneal cavity by increasing the hydrostatic pressure of the peritoneal vessels).

3. **↑ Aldosterone ⇨ Salt & water retention :**
   - In liver failure ⇨ ↓ destruction of aldosterone.
   - Hypoalbuminemia ⇨ hypovolamia ⇨ ↓ RBF ⇨ ↑ renin ⇨ ↑ angiotensin II ⇨ ↑ aldosterone.

4. **<u>Peripheral arterial & splanchnic vasodilatation theory</u> :**

   This is mediated by accumulation of vasodilators (mainly nitric oxide) ⇨ pooling of blood into peripheral & splanchnic arteries ⇨ vascular underfilling is sensed by the kidney ⇨ This leads to activation of the **renin-angiotensin system** ⇨ Salt retention ⇨ Ascites.

5. **<u>Lymphorrhea</u>:** (liver weeping) ♦♦

   Post sinusoidal obstruction → ↑ lymph production into peritoneum.

6. ***Associated factors***: <u>SBP</u>, malignancy, T.B. peritonitis….

<u>Spontaneous bacterial peritonitis:</u> (*SBP*)

- Infection of the peritoneal cavity in absence of known etiology.
- Occurs in 10% of cirrhotic patients.
- Due to loss of detoxification function of the liver.
- The prognosis is very bad.
- c/p :

  i deterioration of liver function, e.g. ↑ encephalopathy, ascites or jaundice.

  ii- resistance to diuretics may be a sign of SBP.

  iii- High fever, sever abdominal pain, tenderness.

NB : Cirrhotic patients with ascites and evidence of any clinical deterioration should undergo diagnostic paracentesis to exclude SBP.

- **Diagnosis :**

  The key of diagnosis is <u>examination of the ascetic fluid</u>.

  - **Neutrophils count > <u>250</u> cells / mm^3.**
  - Culture: monomicrobial e.g. E.cali.

- **Treatment** :

  Cefotaxime: 2 gm t.d.s…IV <u>or</u> **C**iprofloxacin 400 mg/12h for 5 - 10 days.

Clinical picture & Investigations of a case of ascites: see later

Treatment : **6 Item**

1- Salt restriction. < 2 g /d. cornerstone of therapy.

2- Diuretics :

i. Spirnolactone in full dose 100-400mg/ d… drug of choice.

ii. Lasix (40-160 mg/d)

The maximum amount of fluid transported from peritoneum to the blood is 500-700 cc/d, so any more lasix → general dehydration of the body without improvement of ascites. *(ascites without edema LL)*

3- Tapping (paracentesis) : indicated in the following conditions :

- Sampling.
- To relieve respiratory distress.
- To relieve compression on the kidney.

4- Albumin (infusion) : to correct the osmotic pressure of the plasma.

5- Peritoneo-venous shunt : Le Veen shunt.

- To drain the ascetic fluid into the circulation.
- Complications : Septicemia , DIC , Hypervolemia & Heart failure.

6- Treatment of the cause : Antibiotics for SBP , liver transplantation.

- ✓ Ascites must not be treated if there are marked manifestations of liver cell failure e.g. hepatic encephalopathy.
- ✓ **W**et & **W**ise better than **D**ry & **D**rowsy. ☺

Refractory ascites : *Details : see later*

Ascites with lack of response to : 400 mg spironolactone plus 160 mg lasix daily with salt restricted diet for at least one week.

VI. **Skin manifestations:** Due to accumulation of vasodilator material (VDM) e.g. estrogen, Nitric oxide.

1. **Palmar erythema:**
   - Erythema in head of metacarpal bones, thinner & hypothinner with central pallor.
   - Also seen in pregnancy, thyrotoxicosis or RA.

2. **Spider naevi:**
   - Vascular lesions usually found in the distribution of SVC (on the face , trunk & upper part of the arms).
   - They consist of a central dilated arteriole with radiating capillaries.
   - Compression of the central arteriole causes blanching of the radiating capillaries.
   - They are also found in pregnancy.

3. **Paper money skin**:
   Numerous small vessels scattered in skin over bony areas, dorsum of foot & hand, forehead, chest.
4. **White nail:** white zone at the tip of the nail.

VII. **Endocrinal manifestations:** may be due to disturbance of sex hormones

♂
- Gynecomastia.
- Female distribution of suprapubic hair.
- Impotence, ↓ libido & testicular atrophy.

♀
- Amenorrhea & sterility.
- Atrophy of breast & ↓ libido.

- ↑ Aldosterone & ADH (in males & females)

VIII. Cardiovascular manifestations: (VDM)

i- **Hyperdynamic circulation**: due to :

- Anemia.
- Toxic product are vasodilators (VDM)

ii- **Cyanosis & clubbing** : due to

- Opening of intrapulmonary A.V. shunt. → d. to (VDM)
- Porto-pulmnary shunts.
- Basal lung collapse due to ascites.

iii. Cardiac dysfunction : due to

- Neurohumoral hyperactivity (RAAS) leading to myocardium growth and fibrosis with disturbed relaxation.
- An inhibitory effect of circulating cytokines (e.g. nitric oxide) on ventricular function.

This cardiac dysfunction remains clinically silent masked by the afterload reduction that is observed in cirrhosis. So, cardiac reserve may be diminished and acute heart failure may manifest after TIPS or liver transplantation.

IX. Hematological manifestations:

i- Anemia:

- Normocytic normochromic :
  - BM depression by toxins.
  - Hyprsplenism.
- Microcytic hypochromic: Iron deficiency anemia due to chronic Blood loss.
- Macrocytic : Vit B_{12} & folic acid deficiency.

ii- Bleeding tendency: due to

- Hypoprothrombinema.
- ↓ factors II, VII, IX, X (1972)
- Hypersplenism → thrombocytopenia.
- Hypofibrinoginemia.
- ↓ vit. K

X. **Hepato-renal Syndrome:** (HRS)

- Functional renal failure with normal renal histology in patients with advanced liver cirrhosis or fulminant hepatic failure.

- **Pathophysiology** :

  The hallmark of HRS is renal vasoconstriction. The exactly mechanism is unknown, but may be due to :

  1) Peripheral splanchnic arterial vasodilation theory : (*Underfill theory*)
     Splanchnic vasodilatation due to portal hypertension & accumulation of VDM e.g. nitric oxide ⇨ pooling of blood into peripheral & splanchnic arteries ⇨ vascular underfilling is sensed by the kidney ⇨ This leads to activation of the **renin-angiotensin system** ⇨ renal vasoconstriction.

  2) Hypovolemia due to hypoalbuminemia, ascites, diuretics.

  3) Cardiac dysfunction associated with hepatic disease is a recent theory.

- **Criteria of diagnosis** :

  1. Chronic or acute liver disease with advanced hepatic failure & portal hypertension.
  2. Low glomerular filtration rate (serum creatinine >1.5 mg% or 24-hr creatinine clearance <40 mL/min).
  3. Absence of shock or current treatment with nephrotoxic drugs.
  4. No sustained improvement after withdrawal of diuretics & expansion of plasma volume.
  5. No ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

- **Types** :
  - ➲ Type 1 HRS : Rapidly progressive type with high mortality rate. There is a doubling of serum creatinine to a level greater than 2.5 mg/dL in <2 weeks.
  - ➲ Type 2 HRS : Slower progressive course with a serum creatinine of >1.5 mg/dl with better prognosis.

- **Precipitating factors** :
  1. Large volume paracentesis of ascites without volume expansion.
  2. Systemic infections e.g. SBP.
  3. Excessive diuretic therapy.
  4. Diminished intravascular volume e.g. diarrhea.

- **Prognosis** : is very bad.

- **Treatment** :
  - IV albumin (plasma expansion)
  - Systemic vasoconstrictors e.g. somatostatin analogs (octreotide).
  - Liver transplantation is the best choice.

XI. Hepatic Encephalopathy:

Definition :

It's a neuropsychiatric syndrome that is seen in patients with acute or chronic liver cell failure or porto-systemic shunting.

Pathogenesis :

1- **Production of toxic substances :** by the action of bacteria on intestinal proteins

- Ammonia : It interferes with creb's cycle : (glutamic acid $\xrightarrow{NH_3}$ glutamine → ↓ CNS)
- Others : inhibitory neurotransmitters
  e.g. γ aminobutyric acid (GABA), Mercaptan, benzodiazepine like compounds.

2- **Disturbance of amino acids** :

Decreased branched-chain & increased aromatic amino acids leading to :

- Decreased production of normal neurotransmitters (as noradrenaline)
- Formation of false neurotransmitters (e.g. octopamine).

3- **Alkalosis & hypokalemia** :

- ↓ glucose entry to cerebral cells → coma.
- ↑ the renal production of ammonia.
- ↑ the permeability of BBB to some of toxic substances.

Precipitating factors : **6 Items**

1- **GIT bleeding**.
2- ↑↑ protein intake. } ↑ ammonia
3- Old Blood transfusion.
4- Aspiration of ascites.
5- Diuretics : Frusemide *(lasix)* } ↓ K^+ & alkalosis
6- Others :
   - Drugs : Morphine , Benzodiazepines.
   - **S**BP (*spontaneous bacterial peritonitis*).
   - **S**urgery e.g. porto-systemic shunts.

Clinical picture:

- Pre coma: 2 S A D
- Coma

i- Pre Coma: **6 Items**

- **S**leep: Inverted sleep rhythm (day/night reversal), *any metabolic error can do that*.
- **S**peech: slow, slurred or monotonous.
- **A**pathy: slow response to questions.
- **A**sterixis: (*Flapping tremors*).
- **D**isorientation: for time, place, persons.
- **D**isturbed behavior : childish attitude , phasic excitation & depression.

ii- Coma: Irritable coma.

Causes of bilateral astrixis :
- Any organ failure : hepatic, renal, cardiac or respiratory failure.
- Metabolic abnormalities : hypoglycemia, hypokalemia and hypomagnesemia.
- Drugs : alcoholism, phenytoin, barbiturate.
- Wilson's disease.

Unilateral astrixis : focal brain lesion e.g. midbrain, internal capsule.

DD of irritable coma :
Hypoglycemic coma, **H**epatic coma.

Clinical stages of hepatic encephalopathy : (*for postgraduates*)

Stage	Mental status	Asterixis	EEG
I	Mild confusion , slow mentation , inverted sleep rhythm.	+/-	Triphasic waves (5 cycles/sec)
II	- Lethargy. - moderate confusion & disorientation	+	Triphasic waves
III	- Marked confusion & disorientation - Sleepy but responds to pain & voice	+	Triphasic waves
IV	Coma (unrousable, unresponsive to voice & pain).	- (Decerebration)	Delta activity (2 cps)

Diagnosis :

The diagnosis can usually be made clinically, but when doubt exists :

- Electroencephalogram (EEG) : shows diffuse slow triphasic waves.
- Ammonia level : ↑ , It is not a sensitive or specific test for hepatic encephalopathy.

Treatment of hepatic encephalopathy: **6 Items**

1- Hospitalization in ICU, endoscope should be done to localize the site of bleeding.

2- Diet:

- protein: restricted.
- Carbohydrate : ↑↑ ⇨ ↓ protein breakdown as a source of energy.
- Fats in small amount → mild diarrhea which is useful to wash intestine.
- K excess : fruit juices.

3- Enema / 4h ⇨ wash the colon.

4- Antibiotics : to prevent the action of intestinal bacteria on proteins.

- Neomycin 1gm/6h orally. SE : nephrotoxicity or
- Metronidazole : 500 mg / 6h . or
- Rifaximin : 400 mg t.d.s.

5- Lactulose (30 - 120 ml 3 times daily) : oral or rectal.

- Osmotic diarrhea → wash the colon.
- Production of acids . this promotes the conversion of luminal ammonia (NH_3) to ammonium (NH_4)

$$NH_3 + H^+ \rightarrow NH_4 \ (non\ absorbable)$$

6- Liver transplantation.

Drugs of doubtful value :

- **B**ranched amino acids.
- **B**romocryptin & L dopa : to improve neurotransimission.
- **B**enzodiazepine antagonists : Flumazenil.
- L-ornithine L-aspartate (Lola) : it reduces the level of ammonia.

Sedatives :

- Should be avoided, but if necessary; give small doses of diazepam.
- Morphine is absolutely contraindicated.

Investigations of LCF:

- Liver function tests :
  - Serum enzymes (AST , ALT) : ↑
  - Serum bilirubin : ↑ (both direct & indirect)
  - Plasma proteins : ↓ albumin , ↑ globulin (reversed A/g ratio).
  - Prothrombin time : prolonged , not corrected by parentral vitamin K.
- Investigations for the cause :
  - Abdominal US , CT : for cirrhosis.
  - Hepatitis markers : for hepatitis.
- Investigations of ascites.
- Investigations of hepatic encephalopathy.

N.B. *Biopsy is very difficult due to bleeding & Ascites.*

Treatment of LCF:

- Treatment of the cause : if possible.
- Treatment of ascites: provide that the features of LCF are not sever.
- Treatment of encephalopathy.
- Liver transplantation.

ACUTE (Fulminant) HEPATIC FAILURE

Definition:

It's an acute liver failure with rapid development of hepatic **encephalopathy** & **coagulopathy** within 8 weeks in patients without pre-existing liver disease.

N.B:

- Hyper acute liver failure → within 2 weeks.
- Acute liver failure → within 2-8 weeks.
- Sub acute liver failure → 8 weeks - 6 months.

Etiology:

- **Viral hepatitis .**
- **Paracetomal toxicity** (> 15gm = 30 tab)
- Alcohol toxicity.
- Acute fatty liver of pregnancy.

Clinical picture:

- **Encephalopathy** (pre coma & coma)
- **Coagulopathy** : (bleeding)
- **Jaundice** : rare, the disease may develop so rapidly that jaundice is not apparent & the condition may be misdiagnosed as encephalitis .
- The condition usually ends by **death** due to bleeding, cerebral edema, respiratory & circulatory failure (shock) & other organ failure.

Investigations:

i. **Liver function tests :**
   - Serum Bilirubin : Exceeding 23mg → Poor prognosis.
   - Serum enzymes (AST , ALT) : ↑↑
   - Serum albumin : Normal

- prothrombin time : prolonged. (it is used to asses the prognosis)

ii. **Investigations for the cause :**

- Hepatitis markers.
- Serum drug screen e.g. paracetamol.

iii. **CT , MRI of the brain** : to exclude brain lesions.

Treatment:

i. Treatment of encephalopathy.
ii. Treatment of complications.
iii. Artificial hepatic support : Charcoal filter are used to adsorb toxins from the blood.
iv. Hepatic transplantation.

PORTAL HYPERTENSION

Definition:

Elevation of portal venous pressure above 12mm Hg (N: 7-10 mm Hg)

Etiology: The most common cause at all is **Liver cirrhosis**

i- Supra hepatic (Cardiac cirrhosis) e.g.

RSHF, TR, Pericarditis, IVC obstruction & Budd Chiari syndrome.

ii- Hepatic (most common) :

- **sinusoidal & post sinusoidal :**
  - **Liver cirrhosis** "the most common cause".
  - Veno-occlusive disease.
- **pre sinusoidal :**
  - **Sch**istosomiasis (Bilharziasis): peri-portal fibrosis.
  - **C**ongenital fibrosis of portal tract.
  - **H**odgkin's lymphoma, leukemia.

iii- Infra-hepatic : rare

- Portal vein thrombosis (Hepatoma).
- Congenital stenosis of portal vein.
- Extrinsic compression (tumor)

Cirrhosis is the main cause of portal hypertension By:

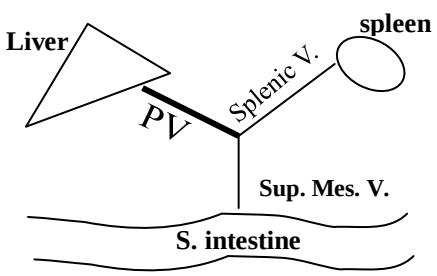
1- The trauma that caused cirrhosis creates an arterio-venous fistula between the hepatic arterioles & portal vein.

2- Liver fibrosis & regenerative nodules increase the portal pressure by compression.

Pathophysiology:

Portal vein is formed by the union of superior mesenteric & splenic veins.

So, portal hypertension leads to:



i. Spleen congestion.
ii. Intestinal congestion.
iii. Porto-systemic shunt : in attempt to decompress the portal hypertension.
   - ➲ Development of collateral channels : esophageal varices, Caput medusa, Hemorrhoids.
   - ➲ Shunting of toxins from the intestine into the general circulation ➝ Hepatic encephalopathy.

Clinical Picture: 6 item

(1) Splenomegaly:

- Dragging pain in the left hypochondrium.
- May be the only clinical evidence of portal hypertension.
- May be associated with hypersplenism, which by turn lead to pancytopenia & bleeding tendency.

No relation between the size of spleen & severity of portal hypertension.

(2) Intestinal congestion:

- **D**istension.
- **D**yspepsia.

(3) Liver: firm & sharp border (*cirrhotic liver*)

(4) Ascites : SAAG > 1.1

Portal hypertension is a localizing factor rather than a cause.

(5) Encephalopathy : - Pre-coma: 2S, 2A , 2D.
- Irritable come.

(6) Porto-systemic shunt: In attempt to decompress the portal hypertension.

Main sites of the collaterals :

Site	Portal Circulation	Systemic C.	Clinical presentation
1- Lower end of esophagus	Coronary veins of stomach	Azygos vein	Esophageal varices with or without bleeding
2- Around the umbilicus	Umbilical vein in flaciform ligament	Veins of anterior Abdominal wall	Caput medusa (flow away from umbilicus)
3- Anal canal	Superior & middle rectal veins	Inferior rectal vein	May be mistaken for hemorrhoids

N.B. Actually piles never occurs, this is because:

- Too far from the portal vein to transmit pressure.
- Perianal sphincter are always in tonic contraction that compress the veins.

(Caput medusa)

Complications of portal hypertension: 6 items

1- Esophageal varices.

2- Ascites.

3- Portosystemic encephalopathy.

4- Hypersplenism.

5- Congestive gastropathy (bleeding)

6- Renal failure.

Esophageal varices :

- Dilated, elongated, tortuous veins located at lower end of the esophagus.

- Etiology : I can say that portal hypertension is the only cause of esophageal varices & no one can blame me !!

- Clinical Picture :

- Approximately 90% of cirrhotic patients will develop esophageal varices, over 10 years, but only ⅓ of these will bleed.
- Bleeding is likely to occur with large varices, red signs on varices (diagnosed by endoscope) and in severe liver disease.

i- before rupture:

- Asymptomatic (silent)
- dysphagia (rare)

ii- At rupture: Upper GIT bleeding

- Painless massive hematemesis.
- Melena.

N.B. Because other etiologies of upper gastrointestinal bleeding are also common in cirrhotics (gastritis, peptic ulcer) variceal bleeding should be confirmed with endoscope (even in patient with known varices).

Investigation of portal hypertension: (esophageal varices)

6 items

1- Endoscopy:

- Detects early varices.(Esophageal varices confirm the diagnosis of portal hypertension)
- Detects signs of impending rupture (red signs).
- Detects active bleeding & its site.
- Can be used for sclerotherapy of varices.

2- Imaging of the portal circulation :

a) Doppler or Duplex ultrasound : Detect pressure , blood Velocity & patency.

b) CT , MRI.

3- Measurement of the hepatic venous pressure gradient : HVPG

(Free & wedged hepatic venous pressure)

- Catheter is introduced into SVC → IVC → hepatic vein (*free hepatic venous pressure*) → then pushed till it is wedged in hepatic sinusoids (*wedged hepatic venous pressure*)
- It is an indirect measurement that closely approximates portal vein thrombosis.

4- Spleno-portography: needle introduced into the spleen → inject dye for patency of portal vein.

5- Evaluation of the liver: liver function tests , liver biopsy.

6- Investigations of Bilharziasis : e.g. Barium enema.

N.B. *Direct portal measurements usually are not performed due to invasive nature.*

Treatment of portal hypertension:

1- Treatment of esophageal varices.

2- Treatment of porto-systemic encephalopathy.

3- Treatment of ascites.

Treatment of esophageal varices:

During attack: *(Control of acute bleeding)* *6 items*

1- **Initial resuscitation** with replacement of blood volume.

2- **Endoscopy** to detect the site of bleeding.

3- **Pharmacological therapy** :

- Vasopressin.
- Somatostatin.
- **Octreotide**.
- Terlipressin.

Vasopressin: (*pitressin*)

- V.C. of mesenteric & hepatic arterioles ⇨↓ Portal inflow ⇨↓ portal vein pressure ⇨↓ Hemorrhage.
- Dose: 20 unit in 200ml glucose 5% over 20 min.
- SE: generalized V.C may result in peripheral vascular ischemia, Ischemic heart disease & hypertension so, we may use nitrate with vasopressine.
- Somatostatin or **octreotide** are more safer.

- ✓ Whatever drug is used, it's inadvisable to continue drug therapy for more than 1 to 2 days.
- ✓ Pharmacological therapy can be initiated as soon as variceal hemorrhage is suspected, even before diagnostic endoscope.

4- <u>Injection sclerotherapy and / or band ligation</u>: (endoscopic therapy)

The efficacy of rubber band ligation is similar to sclerotherapy with fewer complications e.g. esophageal ulceration, stricture, chest pain, aspiration …

5- <u>Sengstaken- Blakemore tube</u> : mechanical compress of esophageal varices.

- ***Diagnostic value* :**

  Used in a case of hematemesis, if the bleeding doesn't stop ⇨ source is not the esophagus.

- ***Therapeutic value* :**

- If bleeding doesn't stop by conservative treatment.
- If endoscope is not immediately available.

S/E: Esophageal perforation & ischemia especially in inexperienced hand.

6- When all the above measures fail, Transjugular intrahepatic portosystemic shunt (<u>TIPSS</u>) or portosystemic shunt operations are considered.

Prevention: 6 item (3 primary , 3 secondary)

1ry prevention (silent varices)

(Prevention of the first variceal bleeding)

1- Small varices: no treatment is required.

2- Large varices:

- β blockers (propranolol) : ↓ COP , splanchnic vasoconstriction.
- Nitrates (isosorbide mononitrate) : venodilator

3- Impending rupture: band ligation (Endoscopic Variceal Ligation , EVL)

NB : *prophylactic injection sclerotherapy has no role in primary prophylaxis.*

Secondary prevention

(Prevention of recurrent variceal bleeding)

1- β blockers (propranolol) : ↓ the risk of rebleeding up to 40%.

2- Repeated injection sclerotherapy or band ligation till varices disappear.

3- TIPS , portosystemic shunt & liver transplant are considered in patient who rebleed during above measures.

- TIPSS (transjugular Intrahepatic porto-systemic shunt):

- Inserting of short metal tube through neck vein (Jugular) → liver (hepatic) & connect portal vein with hepatic vein (porto-systemic).
- It requires only light sedation & local anesthesia.

- Porto-systemic shunts:

* Portocaval. (SE : encephalopathy)
* mesenterico caval.
* lienorenal → minimal encephalopathy.
  → 2 types : Distal (*warren operation*).
  : proximal.

- **HASSAB operation** (minor surgery) : Splenectomy & esophageal devascularzation.

Gastro-Intestinal Bleeding

Upper GIT bleeding:

- Site of bleeding: is proximal to ligament of Treitz. (*distal duodenum*)
- Presentation:
  - Hematemesis
  - Melena
  - Occult blood in stool

Lower GIT bleeding:

- Site of bleeding: is distal to ligament of Treitz.
- Presentation:
  - Hematochezia (*Bleeding per rectum*)
  - Melena.
  - Occult blood in stool.

Hematemesis :

- Vomiting of blood coming from esophagus, stomach & duodenum.
- Blood may be:
  - Red in color: if immediately after bleeding
  - Coffee ground (*Melenemesis*): when blood is in contact with gastric acid for at least 1 hour.

Etiology of hematemesis **:**

Esophageal:

- Esophageal varices.
- Cancer esophagus.
- Esophagitis due to infections , reflux ,..
- Mallory – Weiss syndrome :
  - Mucosal tear due to repeated vomiting.
  - Treatment : self limited, vasopressin may be used.

Gastro-duodenal:

- Duodenal ulcer.
- Gastric ulcer.
- Gastritis.
- Cancer stomach.

Systemic (general) causes:

- Hemorrhagic blood diseases.
- Hemorrhagic fever.
- Severe hypertension.
- Heparin therapy.

Diagnosis of hematemesis:

Remember this word **CIS** : **C**ause - **I**ron deficiency anemia - **S**hock ☺

1- ***History :***

Cause	*Question to detect the cause*
1- Esophageal varices	History of cirrhosis, confusion?
2- Peptic ulcer	Epigastric pain, dyspepsia, heart burn?
3- Gastritis	History of drug intake e.g. Aspirin, Alcohol, NSAID? Epigastric pain?
4- Cancer stomach	Weight loss, Meat dyspepsia
5- Mallory-Weiss.	Preceded by severe vomiting?
6- Coagulation defect	Oral anticoagulant? History of cutaneous or orifice bleeding?

2- ***Examination :***

i. Manifestations of the cause e.g. chronic liver disease.

ii. Manifestations of hypovolemic shock :

- Pallor & cold sweating.
- Low systolic BP < 100 mmHg, Tachycardia > 100/min.

iii. Manifestations of iron deficiency anemia in a case of recurrent bleeding.

3- ***Investigations :***

i. Nasogastric tube: usually +ve for blood

ii. Endoscopy to localize the site of bleeding.

iii. Angiograpy : done if endoscope fails to show the site of bleeding.

iv. Lab : CBC , Liver function tests.

Treatment *of hematemesis*:

1- Resuscitation: IV fluid & fresh blood transfusion if necessary.

2- Endoscopy.

3- Treatment of the cause: e.g.

- Esophageal varices : see before.
- Peptic ulcer : IV Proton pump inhibitor (omeprazole) or H_2 blocker.

4- Iron therapy: given in chronic cases presenting with iron deficiency anemia.

Ø Ø of hematemesis:

- Differentiation of the cause.
- Hemoptysis.
- False hematemesis : Ingestion of blood after bleeding from the nose, mouth or pharynx then vomiting of this blood.

Melena:

- Passage of **black tarry stool** due to presence of digested blood.
- It indicates that hemorrhage has remained for ≥ 8 hours in the GIT
- Site of bleeding : is not merely above ligament of Treitz as hematemsis but may extend up to the right colon. (above the ileocecal valve)

Etiology :

i- Etiology of upper GIT bleeding (hematemesis) *plus*

ii- Jejunum & ileum: 2T + 2C

- **T**.B enteritis
- **T**yphoid ulcer
- **C**ancer head of pancreas.
- **C**rohn's disease.

iii- Colon:

- Ulcerative colitis.
- Right sided tumor.

Ø Ø of dark stool:

- Melena.
- Iron ingestion.
- Hemolytic Jaundice.

Diagnosis & Treatment of melena: *The same as hematemesis.*

Hematochezia:

- Passage of **bright red blood** per rectum.
- Usually indicate that lesion distal to right Colon.

Etiology :

- Anal lesions (Hemorrhoids, fissures).
- **Diverticulosis**.
- Polyps.
- Ulcerative colitis.
- Infectious colitis.
- Colonic Cancer: usually present with chronic occult bleeding.

Diverticulosis is the most common cause of acute lower GI bleeding in patients > 40 years of age.

Diagnosis of Hematochezia:

1. Clinical history.
2. PR examination.
3. Colonoscopy.
4. Barium enema.
5. Nasogastric tube : -ve
6. Lab : Anemia.

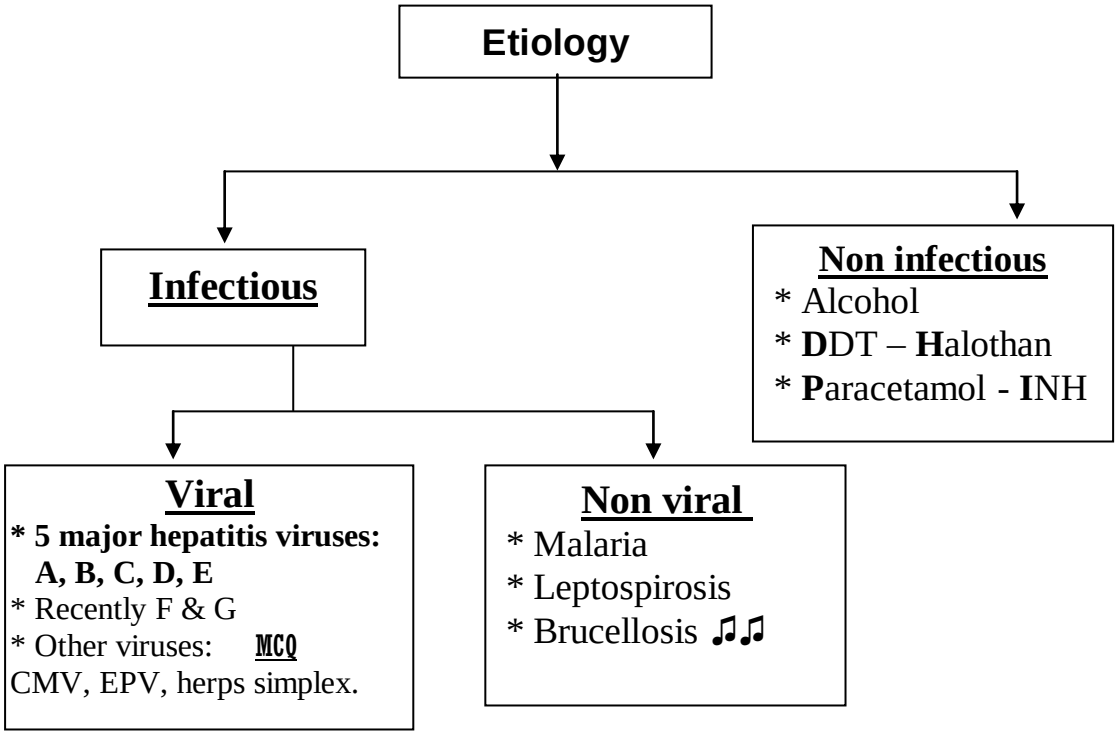
Avoid flexible Sigmoidoscopy and barium enema in the initial stages of diverticulitis because of perforation risk.

Occult GIT blood loss:

Normal appearing stool but hemoccult +ve.

HEPATITIS

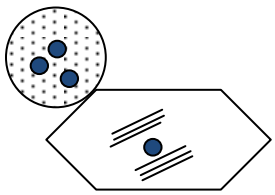
Definition : is an inflammation of the liver



	A	B	C	D	E
Viral genome	RNA	DNA	RNA	RNA (incomplete virus with HBs Ag coat)	RNA
Transmission	Feco-oral	Bodily fluid : Serum (Parenteral) Semen (Sexual) Saliva Transplacental	-Parenteral - sexual : (V.rare, anal only)	Parenteral sexual	Feco-oral
IP	2-6 w	2-6 m	2-6 m	2-6 m	2-6 w
Mortality rate (fulmination)	1%	1%	0.1%	Up to 10%	1% (in pregnant women 20%)
Chronicity	No	5-10% In children : 90%	Up to 85%	50%	No
Malignancy	No	Yes	Yes	Yes	No
Prophylaxis :					
Immunoglobulin:	Non specific	Specific	-	-	-
Vaccine :	Yes (*havrix*)	Yes : 0,1,6 month	No	No (vaccination against HBV)	No

Pathology of acute viral hepatitis:

Hepatic pathology:



- Portal tract infiltration with inflammatory cell.
- Centrizonal necrosis & central cholestasis.
- Healthy frame work.

Extrahepatic pathology:

Splenomegally, lymphadenopathy, nephritis, vasculitis, bone marrow depression, arthritis…..

Clinical picture of acute hepatitis:

1- *Non-icteric hepatitis:*

- Mild form of hepatitis without jaundice.
- S. bilirubin < 2.5 mg %.
- Clinically it presents by influenza like symptoms: Fever, Headache, Malaise, Anorexia (*FHMA*). So it is usually missed in diagnosis.
- Fate of not-icteric hepatitis.

Resolution — chronic hepatitis (*cryptogenic cirrhosis*)

2- *Icteric hepatitis:* passes through 3 stages

i- pre-Icteric stage: (*viremia*) 3-10 days.

- Acute onset of fever (*with relative bradycardia*), headache, malaise , anorexia and there may be nausea & vomiting.
- **Anorexia** is marked especially towards cigarettes & alcohol.
- Dull aching pain in Right Hypochondrium (*enlarged tender liver*)

ii- Icteric stage: 2-4 weeks

- Jaundice appears with improvement of general condition (↓ FHMA).
- Dark urine occurs at first followed by pale stool & then scleral ictrus.
- Jaundice is due to swelling of hepatocytes → obliteration of bile canliculi.
- Liver is enlarged, tender & soft.
- Spleen is mildly enlarged (*just palpable* spleen).
- LN : slightly enlarged cervical LN may occur in about 10% of cases.

DD of just palpable spleen:

- Hepatitis - Typhoid - Brucellosis - SBE - IMN - Grave's disease.

iii- Post icteric: (*Convalescence stage*): 3- 6 months

- Symptoms & signs gradually disappear.
- S. bilirubin ↓↓ but jaundice still present for some time *(bilirubin has high affinity to collagen elastic fibers especially in sclera).*
- Within 3-6 months, patient become clinically and biochemically free.

Sequelae of hepatitis: i. Complete recovery ii. Complications

i. *Complete recovery :*

- All cases of HAV, HEV.
- Many cases of HBV.
- Few cases of HCV.

ii. *Complications :* 6 items

1- **Relapse**: clinical or biochemical relapse.

2- **Acute fulminant hepatitis**:

- Rare condition in which there is rapid development of fulminant (*acute*) hepatic failure (*encephalopathy & coagulopathy*).
- May develop so rapidly that jaundice is not apparent so, the condition may be misdiagnosed as encephalitis. *(details : see acute liver cell failure)*

3- **Prolonged cholestasis:** "*watson's syndrome*"

- Due to unresolved edema of hepatocytes → close bile canaliculi → jaundice deepens with pruritus.
- This condition may occur especially with hepatitis A.
- The condition resolves within 8-28 weeks.

4- **Post hepatitis syndrome**: *may be psychic ?*

- Here, the patient is still complaining (fatigue, anorexia & pain in Right Hypochondrium) even after recovery.
- Liver function tests & liver biopsy are normal but, transaminases may be raised (*transaminitis*).

5- **Chronic complications:** only in hep. B, C, D

- **C**hronic hepatitis.
- **C**irrhosis.
- **C**ancer.
- **C**arrier. (+ve hepatic markers , -ve hepatic enzymes)

6- **Extrahepatic complications:** (*immune complex manifestations*).

I. **Hematological** :

- Essential mixed cryoglbulinemia : (EMC) Details : see hematology book
  - ✓ Medical condition in which the blood contains large amounts of cryoglobulins - *proteins that become insoluble at reduced temperatures.*
  - ✓ Hepatitis C can be found in 95% of all patients with EMC.
  - ✓ C/P : Rash, arthralagia, splenomegaly & muscle weakness.
  - ✓ Interferon : leads to symptomatic improvement of both rash & joint pains.
- Lymphoma :
  - ✓ There is an increased incidence of B cell lymphoma in patients with hepatitis C.
  - ✓ Lymphadenopathy & unexplained chronic anemia in a patient with hepatitis C infection should raise the possibility of lymphoma.

II. **Renal** :

- GN : The most common histological lesion is membranoproliferative GN.

III. **Dermatological** :

- Porphyria cutanea tarda : (PCT)

  It is the most common form of porphyria. The disorder results from low levels of the enzyme responsible for the fifth step in heme production.

- Lichen planus : is a chronic mucocutaneous disease that affects the skin, tongue, and oral mucosa.

IV. **Endocrine disorders** :

- DM : Hepatitis C increases the incidence of type 2 DM 3 times.
- Thyroid dysfunction : due to increased antithyroid antibodies.

V. **Neurological** :

- Peripheral neuropathy : especially mononeuropathy multiplex.
- Encephalitis & encephalomyelitis.

VI. **Eye** :

- Uveitis.
- Corneal ulcer.

VII. **Others** :

- Sialadenitis : inflammation of salivary gland.
- Polyarteritis nodosa.
- Pancreatitis.
- Idiopathic pulmonary fibrosis.

Investigations: 6 items

1- **Urinalysis :** (*bedside test*)

- Dark frothy urine due to early appearance of bilirubin & bile salts.
- Urobilinogen is variable.

2- **Stool analysis:**

- ↓↓ stercobilinogen.
- Pale stool with steatorrhea.

3- **Blood picture**:

leucopenia with relative lymphocytosis due to bone marrow depression.

4- **Abdominal ultrasonography (US)** : diffuse hepatomegaly.

5- **Liver function tests:**

- ALT & AST : Dramatically ↑↑.
- Serum bilirubin: ↑↑ (direct & indirect).
- Alkaline phosphatase: moderate ↑↑.
- Albumin: normal.
- Prothrombin time : Prolonged in severe cases, as all clotting factors except factor VIII are produced by the liver.

6- ***Hepatitis markers***: (*serology*)

Hepatitis A markers:

- HAV antigen : in stool only (*rarely used*).
- HAV antibodies: IgM → recent infection. (Ig**M** ⇨ **M**odern, **M**other ☺)

IgG → old infection (Ig**G** ⇨ **G**randmother ☺)

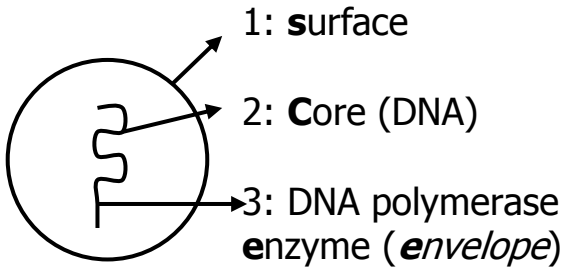
Hepatitis B markers:

There are 3 antigens:

1- HBs Ag

2- HBc Ag

3- HBe Ag



So, 3 Ag + their 3 Ab = 6 markers

HBs Ag: *First marker of infection* **MCQ**

- Appears in blood about **6** weeks after infection.
- Disappears after **3 - 6** months.
- If present longer than **6** months = chronic hepatitis or carrier.

HBsAb:

- Appear in blood after about 3 months & persists.
- If +ve = immune so, no need for vaccine.

Window gap (W.G): is the period ( ) disappearance of HBsAg & appearance of HBsAb.

HBcAg:

Found *only* in hepatocytes & *not* in blood.

HBcAb: (IgM & IgG)

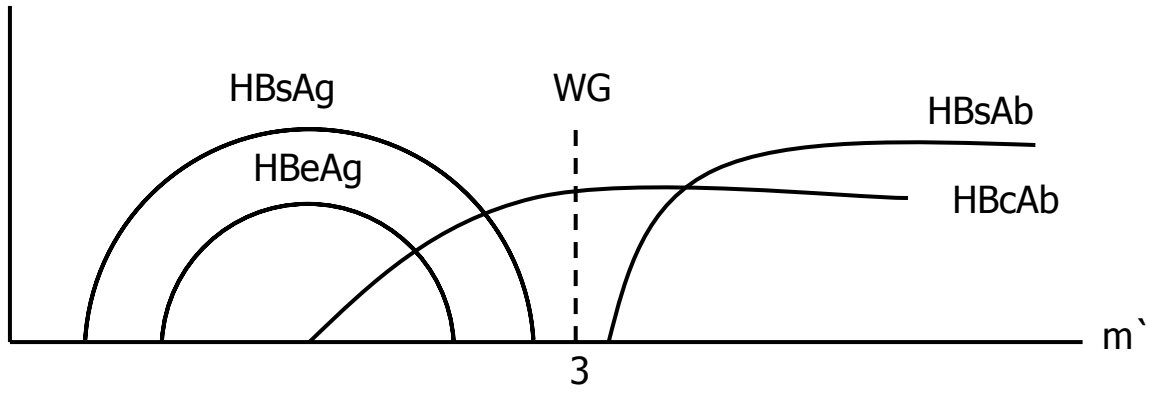
- HBcAb IgM :
  - Acute hepatitis B (*high titre*) , may be +ve during the window gap.
  - Chronic hepatitis B (*low titre*)
- HBcAb IgG : is a lifelong marker indicates past exposure to Hepatitis B. *It does not signify immunity or previous vaccination*.

HBeAg:

Appears shortly after HBsAg in the serum and its persistence is indicative of active viral replication and a high degree of infectivity. (**BE**ware ☺)

HBeAb:

It indicates low infectivity.



	Good prognosis	Bad prognosis
HBsAg	-ve	+ve
HBsAb	+ve	-ve
HBeAg	-ve	+ve
HBeAb	+ve	-ve

HBV DNA : by PCR: it is the most sensitive index of viral replication.

Use of HBV markers in clinical practice :

Test	Acute hepatitis B	Resolved acute hepatitis B	High-replication chronic HBV	Low-replication chronic HBV	Vaccination
HBsAg	+	-	+	+	-
HBeAg	+	-	+	-	-
Anti-HBs	-	+	-	-	+
Anti-HBe	-	+	-	+	-
IgM anti-HBc	+	-	+	-	-
IgG anti-HBc	-	+	+	+	-
HBV DNA	$>10^5$ copies/milliliter	Negative	$>10^5$ copies/mL	10^2 - 10^4 copies/mL	Negative
ALT/AST	+ + +	Normal	+ + +	Normal	Normal

Hepatitis C markers:

- HCV antibodies(IgM, IgG) by ELISA or RIBA: detected after 6 weeks of infection.
- HCV RNA by PCR : detected after 2 weeks of infection.

Hepatitis D markers:

- HDV antibodies: IgM, IgG.
- HBsAg: +ve.

Hepatitis E markers:

HEV antibodies: IgM, IgG.

Treatment : 6 items (3 prevention, 3 therapeutic)

I- Prevention:

1- General measures:

- Hygienic measures especially in hepatitis A,E.
- Supervision of blood transfusion especially in hepatitis C, B, D.

2- Immunoglobulins: as soon as possible after exposure.

3- Vaccine:

- HAV → Havrix.
- HBV → hepatitis B vaccine (0, 1, 6, m`), given to groups at high risk:
  - **H**ealth professionals (doctors, nurses).
  - **H**omosexuals.
  - **H**emodialysis patients.
  - **H**emophiliacs: patient requiring repeated transfusions.
  - **H**ousehold contacts of HBV patients.

II- Therapeutic treatment:

1- Rest: until the patient becomes clinically & biochemically free (bilirubin < 1.5 mg%)

2- Diet:

- Highly appetizing diet.
- CHO : ↑.
- Proteins: free but should be restricted if manifestations of LCF appear.
- Fat : low fat diet is preferred (nauseating).
- Multi vitamins.
- Alcohol: No.

3- Symptomatic treatment:

- Anti-emetics : for nausea & vomiting.
- Cholestyramine : for itching.
- Treatment of complications: e.g. acute fulminant hepatitis.

Cortisone is contraindicated, but may be indicated in a case of prolonged cholestasis.

Chronic hepatitis

Chronic hepatitis is defined as any hepatitis persisting for longer than 6 months.

Etiology:

1- **I**nfections: viral hepatitis (B.C.D).
2- **I**mmune: autoimmune (lupoid) hepatitis.
3- **I**atrogenic: Alcohol ,methyldopa, INH.
4- **I**nherited: Wilson's disease, α1 antitrypsin deficiency.

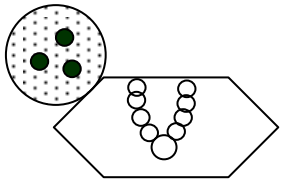
Types:

- Chronic persistent hepatitis (mild form).
- Chronic active hepatitis (severe form).

Chronic persistent hepatitis mild form

Pathology:

- It's a benign inflammatory reaction characterized by just infiltration of the portal tract by inflammatory cells.
- No loss of architecture.



Clinical picture:

- Asymptomatic: discovered accidently &
- May be non specific symptoms: fatigue, anorexia.
- Liver may be mildly enlarged & tender.
- No cirrhosis.

Investigations:

- Liver function tests: are often normal except for elevated transaminases.
- Biopsy: to exclude chronic active hepatitis.
- Investigations for the cause : hepatitis markers.

Treatment:

- Because of its benign nature, treatment is not indicated.
- Just reassurance & follow up / 6 months.

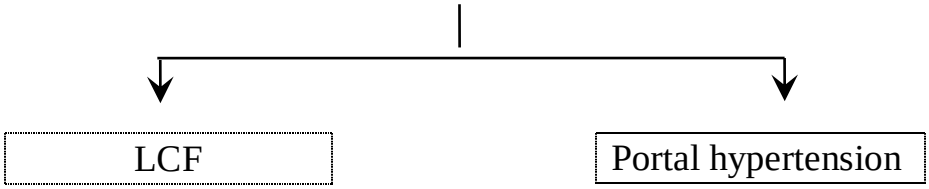
Chronic Active hepatitis

Clinical picture :

- It's mainly viral or autoimmune.
- Progression to cirrhosis is common.

Viral :

- More common in ♂.
- May be asymptomatic for decades , **fatigue** is a common symptom.
- Features of hepatitis : Anorexia , Jaundice , tender liver ….
- Features of chronicity (late) = (features of liver cirrhosis)



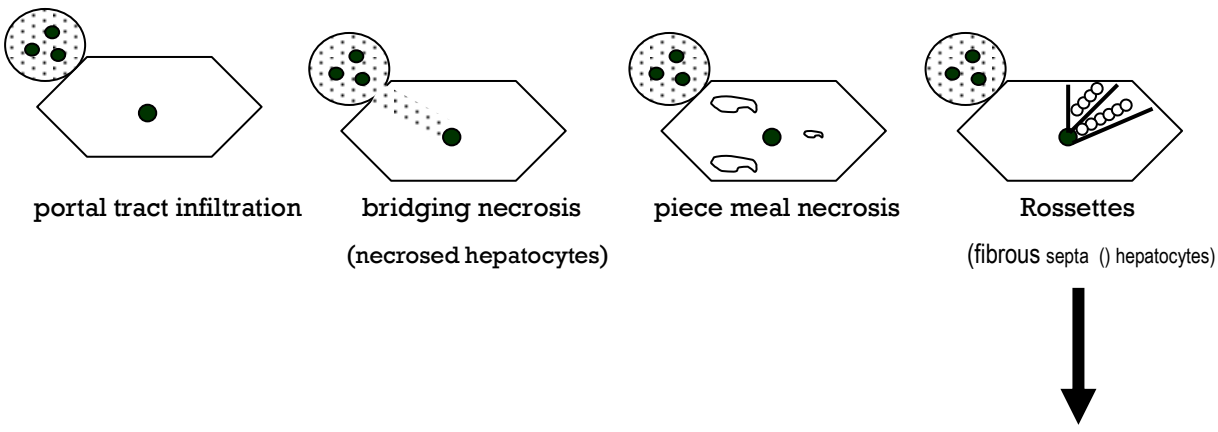
Auto Immune (*lupoid hepatitis*)

The same as viral but :

- more common in ♀. ☺
- some associated manifestations may be present as **H**ashimoto's thyroiditis , **H**emolytic anemia , **P**olyarthritis , **P**leurisy.

Investigation:

i- **Biopsy :** is diagnostic.



ii- **Liver function tests:**

- SGOT, SGPT : ↑ 3-5 folds.
- Serum bilirubin : ↑ (direct & indirect).
- Alkaline phosphatase : ↑ moderately.
- Albumin : ↓
- Hepatitis markers for hepatitis B, C, D.
- **ANA, anti smooth muscle Ab in autoimmune hepatitis**. MCQ

An AST/ALT ratio > 2 suggests alcoholic hepatitis.

Treatment:

I-Treatment of chronic active viral hepatitis:

Goals of treatment :

- Clearance of HBV DNA.
- HBeAg and HBsAg seroconversion (antigen disappearance and appearance of antibodies)
- Normalization of liver enzymes.
- Normalization of histology.

1-Interferon :

dose:

- **Alpha-interferon :**
  - **HBV** : 5 million units SC 3 times/week for at least 3 months.
  - **HCV** : 3 million units SC 3 times/week for at least 6 months.
- **Peginterferon** (*Peg interon*) : Long acting Interferon

  180 µg SC , once/week for at least 6 months.

Side effects:

- Expensive.
- Initial response is 50% of cases.
- Relapse occur in 50% of cases.
- Influenza like symptoms (FHMA).
- BM depression.
- Mental depression.
- ↑↑ hepatic inflammation so not used in severe late cases.

Monitoring :

1- PCR : If no response after 3 months : stop the drug

2- CBC : Stop the drug if WBCs < 3000 or platelets < 100000 /cmm

3- The patient must be monitored carefully for side effects including : flu-like symptoms, depression, BM depression, …

2-Other antiviral agents:

- **Ribavirin**
  - 400 mg twice daily , oral, is added to interferon for HCV. (*good response*)
  - Renal failure is an absolutely contraindication for ribavirin.
- lamivudine : is added to interferon for HBV.

II-Treatment of autoimmune hepatitis:

Predinsolone :

- 1st week : 30 mg/d then maintenance dose 15 mg/d for 6 months - 3 years.
- If full remission → withdraw drug slowly.
- If no remission → continue maintenance *plus* **Azathioprine** (Immuran) 50 mg/d

III. Liver transplantation :

May be indicated in advanced viral disease, but disease recurrence is frequent.

A doctor must work eighteen hours a day and seven days a week. If you cannot console yourself to this, get out of the profession.

Martin H. Fischer

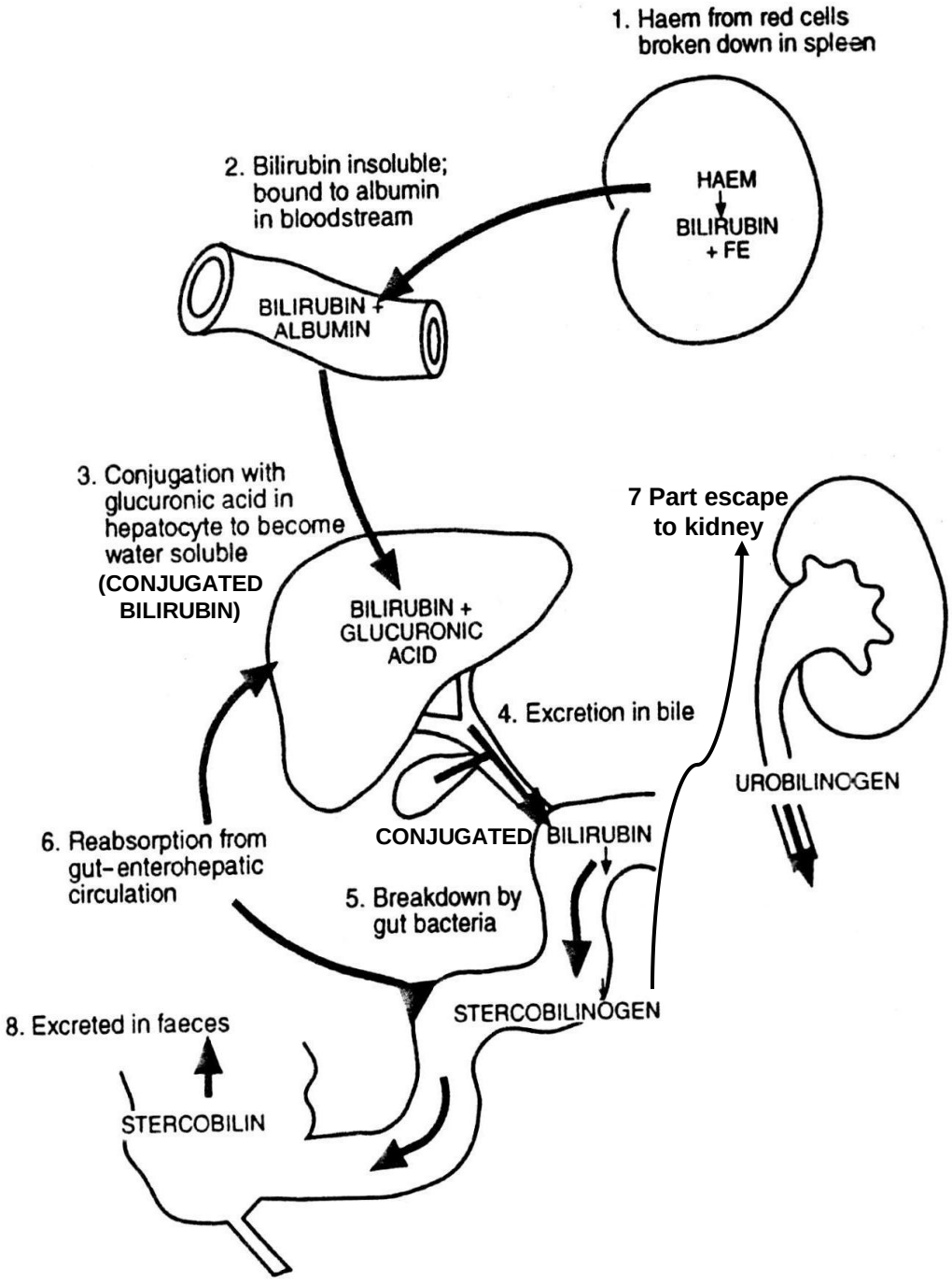
Jaundice

Derived from French word meaning yellow

Definition:

Yellowish discoloration of the skin, sclera & mucous membrane due to ↑ serum bilirubin > 3mg % (N = 1mg%)

Life story of bilirubin:



Causes of Jaundice:

I- Pre-hepatic : (↑ unconjugated bilirubin)

- Excess production of bilirubin or failure of uptake or conjugation in the liver.
  - **Hemolysis (Hemolytic Jaundice).**
  - Glibert's syndrome.
  - Grigler- Najjar syndrome.

II- Hepatic (Hepatocellular): ↑ both conjugated & unconjugated bilirubin.

(Defect is at level of hepatocyte)

- All causes of liver cell failure e.g. viral or drug induced hepatitis.
- Dubin-Johnson & Rotor syndromes : ↑ conjugated bilirubin.

III- Post-hepatic (obstructive, Cholestasis): ↑ conjugated bilirubin.

There is impaired excretion of bile from liver into the gut.

- Extrahepatic:

- **Gallstones**.
- Cancer head of pancreas.
- Enlarged LN in portahepatis.
- Stricture of the wall of the biliary tree.

- Intrahepatic:

- 1ry biliary cirrhosis. - Drugs: e.g. estrogen, OCP, Chlorpromazine.
- Intrahepatic cholestasis of pregnancy.
- Causes of Hepatic jaundice. (see above)

Syndrome	*Genetics*	*Defect*	*C/P*	*Treatment*
Glibert's	AD	Defect in uptake	Asymptomatic ± Jaundice, increases with fasting	Nil as benign condition
Grigler-Najjar ***Type I***	AR	Both due to defect in conjugation (↓ glucuronyl transferase)	neonatal kernicterus & death	None, fatal
Type II	AD		Survive to adulthood	- phenobarbitone - liver transplant
Dubin-Johnson	AR	- Defect in excretion - Brown pigment in hepatocytes.	Jaundice ± right upper guardant pain & malaise	Nil as benign condition
Rotor	AD	- Defect in excretion - No pigmentation in hepatocytes.	Like dubin-Johnson	Nil as benign condition

	Hemolytic jaundice	***Obstructive Jaundice (cholestatic j)***	***Hepatocellular Jaundice***
Pathogenesis	- ↑ hemolysis of RBCs → ↑ hemobilirubin. - The liver can't uptake hembilirubin completely, so part of it is retained in the blood → ↑ serum bilirubin → jaundice. - Large part of hembilirubin is converted into conjugated bilirubin & excreted by i liver→ ↑ stercobilinogen→**dark stool**. - Also ↑ stercobilinogen → ↑ urobilinogen which is colorless So urine is normal in color **(acholuric jaundice).**	- ↓ excretion of conjugated bilirubin into intestine due to obstruction → ↓ stercobilinogen → **pale stool.** - Conjugated bilirubin regurgitates into the blood → ↑ serum bilirubin → Jaundice. Conjugated bilirubin is water soluble so appears in urine → **dark urine** N.B.: - ↓ bile excretion into intestine → steatorrhea. - Bile salts regurgitate into blood & appear in urine.	- ↓ uptake, ↓ conjugation, ↓ excretion of bilirubin. - ↓ uptake → ↑ **unconjugated bilirubin.** - ↓ excretion → ↑ **conjugated bilirubin → dark urine.** - ↓ excretion → ↓ stercobilinogen → **pale stool.** N.B: In HC. Jaundice: ↓ ↓ enterohepatic circulation of stercobilinogen so, urobilinogen is increased inspite of ↓ ↓ stercobilinogen.
investigations	1- ***In serum***: ↑ unconjugated bilirubin. 2- ***In stool***: ↑ sterocobilinogen. 3- ***In urine***: ↑ urobilinogen : Bilirubin is absent N.B: Bilirubin never > 5mg% in Haemolytic Jaundice as long as liver is normal.	1- ***In serum***: ↑ conjugated bilirubin ↑↑ cholesterol. ↑↑ alk. Phosphatas***e.*** 2- ***In stool***: ↓↓ sterocobilinogen. 3- ***In urine***: ↓ urobilinogen : Bilirubin is present	1- ***In serum***: ↑ both conjugated & unconjugated bilirubin. 2- ***In stool*** : ↓ sterocobilinogen. 3- ***In urine***: ↑ urobilinogen : Bilirubin is present
Clinical picture	1- Jaundice: mild (lemon yellow) 2- Urine: Normal 3- Stool: dark 4- Features of hemolytic anemia	1- Jaundice: deep (*olive green*) 2- Urine: dark 3- Stool: v.pale 4- Other features of obst. Jaundice: - Steatorrhea. - **P**ruritis - xanthelasma - **B**radycardia - **b**leeding - **B**one affection: osteomalacia - **Prolonged cholestasis→ cirrhosis**	1- Jaundice: orange yellow. 2- Urine: dark 3- Stool: pale 4- Features of liver failure.

How to reach a diagnosis of a case of jaundice?

I- History taking **II- Physical examination** **III- Investigation**

I. History taking:

Personal history:-

- Age :
  - Child: hemolysis.
  - Adult: hepatitis.
  - Old: cancer head of pancreas.
- Sex :
  - ♂ : Cancer head of pancreas, hepatitis.
  - ♀ : Stones
- Habit : e.g. : Alcohol → hepatitis

Complaint:

Yellowish discoloration of skin & mm.

Present History:

1- Onset:

- **Acute**: hepatitis, stone.
- **Gradual**: malignant obstruction, cirrhosis.

2- Course:

- **Progressive**: malignant obstruction.
- **Regressive**: hepatitis.
- **Intermittent**: Stone.

3- Duration:

- **Short** : hepatitis.
- **Long** : cirrhosis & exclude malignancy.

4- Urine:

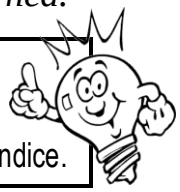
- **Dark** : obstructive & hepatocellular jaundice
- **Normal**: Hemolytic Jaundice.

5- Stool:

- **Dark** : hemolytic Jaundice.
- **Pale**: obstructive & hepatocellular Jaundice.

Stool in obstructive Jaundice is very pale with features of steatorrhea.

Just remember one word : **the urine is not dark in hemolytic jaundice**.
Repeat it 3 times daily .....
The urine is not dark, so the stool is dark ..& the opposite in obstructive & hepatocellular jaundice.



6- Fever:

- Hepatitis (pre icteric phase)
- Low grade fever in cirrhosis, malignancy.

7- Vomiting:

- Early viral hepatitis.

8- Pain:

- Right hypochondrium radiate to right shoulder → stone.
- Epigastric pain radiate to back → cancer head of pancreas.

9- Pruritus:

- Obstructive Jaundice.

10- Marked loss of weight: malignancy.

Past history:

- Hemolytic crisis
- History of drug intake.
- History of biliary colic.
- History of hepatitis & bilharziasis.

Family history:

- Heamolysis.
- Glibert's syndrome.

II- Physical examination:

a) General manifestations:

1- ***C****olor of Jaundice:*

- Hemolytic: Lemon yellow
- Obstructive: olive green.
- Hepatocellular: Orange yellow

2- ***C****achexia*: in malignancy

3- **S**kin manifestations of hemolytic Jaundice: leg ulcers

4- **S**kin manifestations of obstructive Jaundice: Itching, xanthalasma

5- **S**kin manifestations of Hepatocellular Jaundice (LCF): …..

6- **S**kin pigmentation & clubbing: in 1ry biliary cirrhosis.

7- **S**ubcutaneous hemorrhage (Ecchymosis):

- Hepatocellular : due to ↓coagulation factors.
- Obstructive Jaundice : due to ↓ absorption of vit.k.

b) Abdominal examination:

1- Liver:

- Enlarged, soft & tender: viral hepatitis.
- Firm with sharp border: cirrhosis.
- Enlarged, hard, tender & nodular : malignancy.

2- Spleen: enlarged in hemolytic anemia, cirrhosis, hepatitis.

3- Ascites:

- Liver cell failure
- Cancer head of pancreas.

4- gall bladder: (*Courvoisier's law*)

- In obstructive Jaundice:

- Stone: **non palpable** gall bladder. (*due to fibrosis)*
- Cancer: **palpable** gall bladder.

III- Investigations: **5** Lab, **5** imaging, **5** instrumental 3 x ✋

a) Laboratory investigations:

1- ***Liver function tests*** :

	Unconjugated bilirubin	***Conjugated bilirubin***	***SGOT & SGPT***	***Alk. Phosph.***	***Stercobilinogen***	***urobilinogen***
Hemolytic	↑↑	normal	normal	normal	↑	↑
Hepatocellular	↑	↑↑	↑↑↑	↑	↓	↑
Obstructive	normal	↑↑	Normal or ↑	↑↑↑	↓	↓

2- **Blood picture**: features of hemolytic anemia.

3- **ESR**: marked ↑↑ in malignancy.

4- **Serological tests**: Hepatitis markers, autoantibodies.

5- **Therapeutic test**:

- Vit K injection to differentiate between obstructive & hepatocellualr jaundice : Vit K corrects the prothrombin time in obstructive Jaundice, not in hepatocellular Jaundice.
- Cortisone test : to differentiate between intra & extra cholestasis.

Isolated hyperbilirubinemia :
(↑ bilirubin, normal AST & ALT, and alkaline phosphatase).

I. Unconjugated :
   - Hemolytic anemia. (overproduction)
   - Gilbert's syndrome.
   - Crigler-Najjar syndrome.

II. Conjugated : Dubin-Johnson-Rotor syndrome.

B- Imaging:

1- **x-ray**: gall stones.

2- **Barium**: - Swallow: esophageal varices.

- Meal: wide C duodenum in cancer head of pancreas.

3- **U/S** 4- **CT** 5- **Isotopic scan**

C- Instrumental:

1- **ERCP**: (*Endoscopic Retrograde Cholangio – Pancreatography*) is used to investigate obstructive Jaundice & remove obstructing gallstones.

2- **PTC**: (*percutaneous Transhepatic Cholangiography*) indicated in obstructive Jaundice with intrahepatic biliary dilatation.

3- **Liver biopsy**: after correction of bleeding tendency.
   - Technically difficult if ascites is present.

4- Laparoscopy.

5- Laparotomy.

Treatment of Jaundice:

Since Jaundice is a symptom, not a specific disorder, treatment for it **depends on its cause**. This can range from the removal of gall stones or tumors to antibiotics to treat infections, to liver transplant in cases where the liver is severely damaged. However, for conditions like cirrhosis & chronic hepatitis, which are lifelong problems, Jaundice may be permenant or recurrent.

N.B: **Causes of recurrent Jaundice:**

1- Hemolytic crisis

2- Gall stones → recurrent obstructive Jaundice.

3- Recurrent hepatitis.

4- Recurrent cholestasis of pregnancy.

5- Drug induced Jaundice:-

- **Hemolytic:**
  - Drug caused hemolysis: sulpha, ∝ methyl.dopa.
  - Rifampicin: ↓↓ uptake of bilirubin.
- **Hepatocellular:**
  - **D**DT, **H**alothan, **p**aracetamol – **I**NH
- **Obstructive:**
  - **A**nabolic steroid, **P**AS, **c**hlorpromazine , **D**indivan, **E**rythromycine

POST OPERATIVE JAUNDICE :

Definition : Jaundice occurring for the first time in the post operative period.

Etiology :

a) Unconjugated hyperbilirubinemia :

1- Massive blood transfusion or mismatched blood.

2- Absorption of residual hematomas.

b) Hepato-cellular damage :

3- Septicemia

4- Drug induced liver jaundice e.g. Halothane.

5- Viral hepatitis.

6- Activation of pre-existing liver disease.

c) Extra-hepatic obstruction :

7- Missed stones.

8- Post operative pancreatitis.

9- Injury to the common bile duct.

10- Sclerosing cholangitis.

Sclerosing cholangitis :

- Term used to describe fibrous thickening of the bile duct wall associated with multiple strictures.
- It may occur secondary to congenital lesion , operative trauma or no etiology is evident (*1ry sclerosing cholangitis*)

	Intra-hepatic cholestasis	**Extra-hepatic cholestasis**
I . History :		
o Drugs & alcohol:	+	-
o Viral hepatitis :	+	-
o Pain :	-	+
o Duration :	Usually long	Usually short
II. Examination :		
o Liver size :	±	+++
o Spleen :	±	-
o G.B. :	-	±
o Ascites :	±	-
III. Investigation :		
o US :	Constriction of intra-hepatic bile radicals.	Dilation of intra-hepatic bile radicals.
o Cortisone test :	+	_

	Calcular obstruction	**Malignant obstruction**
I. History :		
o Age & sex :	Female , 40 Y	Male , 60 Y
o Onset :	Acute	Gradual
o Course :	Intermittent	Progressive
o Duration :	Long	Short
o Pain :	Colicky in the right hypochondrium radiating to the right shoulder.	Epigastric pain radiating to the back , relived when the patient lies on his belly & exaggerated when the patient lies on the back.
II. Examination :		
o General :	Moderate state	Bad state , loss of weight
o Liver :	Enlarged , smooth	Enlarged , may be nodular. Usually enlarged
o G.B. :	Usually not enlarged	In late cases
o Ascites :	-	May be felt .
o Abdominal mass :	-	
III. Investigations :		
o Amylase	-	+++

Hepatic Bilharziasis

Etiology :

S. mansoni is responsible for 85% of cases, while S. hematobium is responsible for 15%.

Life cycle :

Adult warm in portal vein ⇨ Ova in urine or stool ⇨ miracidia in water ⇨ sporocysts in snails ⇨ cercaria in water ⇨ infect man by skin penetration ⇨ circulatory system ⇨ adult worms in portal vein.

Pathogenesis:

Ø Ova reach liver through portal vain tributaries

⇩

Lodged in portal tracts

⇩

These ova induce cell mediated immune reaction with formation of granuloma (ova surrounded by lymphocytes, macrophages & esinophils)

⇩

Periportal fibrosis.

⇩

Pre-sinusoidal portal hypertension.

In pure Ø → Liver fibrosis & not cirrhosis. (Patients with Ø usually develop cirrhosis mostly due to post hepatitis cirrhosis).

Clinical picture : 4

1- History of Bilharzial dysentery (……)

2- **Portal hypertension** (…….)

3- Liver cell failure → very rare as the hepatic architecture is normal in pure bilharziasis. It may occur in **mixed pathology** e.g. hepatitis C.

4- Pulmonary hypertension & cor-pulmonale may be present.

Characteristic facies :

i. Wasted dehydrated in upper part of the body , while ascites in mid and edema of lower limbs (*spider man*).
ii. Parotid enlargement , anemia due to malnutrition, bleeding & hypersplenism.
iii. Jaundice : very rare & mild.

Liver : Enlarged liver in early cases, NOT tender (*except in associated hepatitis or amebic abscess*), NOT nodular. Later on become shrunken.

Spleen : Enlarged and may reach a huge size : first due to reticulo-endothelial hyperplasia and later due to portal hypertension.

Ascites : may develop late due to associated hypoalbuminemia.

Causes of associated hypoalbuminemia

1. Decreased intake : nutritional deficiency.
2. Decreased absorption : Malabsorption due to intestinal congestion.
3. Decreased production : due to associated cirrhosis in mixed pathology.
4. Increased loss : Bleeding, Protein losing enteropathy.

Stages of hepatic bilharziasis : 4 stages

1-Hepatomegaly.

2-Hepatosplenomegaly.

3-Shrunken liver & splenomegaly.

4- Shrunken liver, splenomegaly & ascites.

Investigation:

1- Investigations to detect bilharziasis (*see Bilharzial dysentery*)

2- Investigations for portal hypertension

3- Liver function tests: +ve if there is mixed pathology in the liver.

4- Investigation for pulmonary corpulmonale: X ray, echo

Treatment:

1- Anti B (see B dysentery) **2- Treatment of portal hypertension.**

3- Treatment of liver cell failure. 4- Treatment of corpulmonale.

Amoebic liver abscess

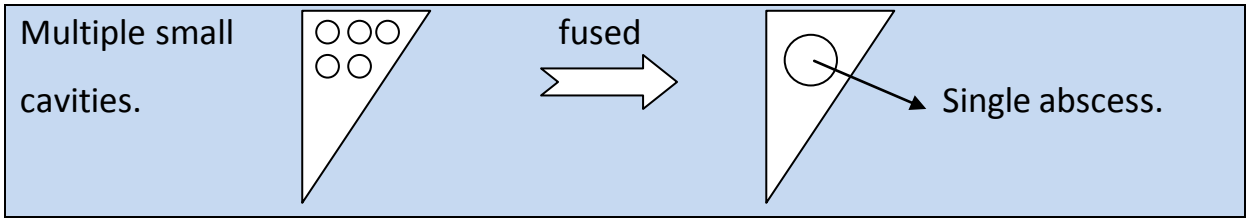
(*Amoebic Hepatitis*)

Etiology:

- Entamaeba histolytica (*vegetative form*) reaching the liver from the colon through portal vein.
- Amoebic dysentery is present in only 50% of cases.

Pathogenesis:

Amoeba reaches liver through portal vein tributaries → foci of necrosis.



Contents of the abscess :

Necrotic tissue + RBC ± pus cells with 2ry infection (*Anchovy Sauce – chocolate material*)

Clinical picture :

1- History of amoebic dysentery. (.....)

2- Features of hepatitis : *but there are* ***:***

- Severe toxemia : fever with rigor, toxic face.
- The liver is enlarged & **tender**.
- Jaundice is usually absent & if present, it's due to obstruction of bile ducts by the abscess.

Don't forget : 3Ps
Pyrexia.
Pain.
Pleural effusion.

3- Complications : spread & rupture

- Right **p**leural effusion, lung abscess.
- **P**ericarditis.
- **p**eritonitis.
- Cutaneous amoebiasis.

Ø Ø :

i- ***Causes of enlarged tender liver*** :

*Inflammation: all except Bilharziasis , $yphilis.

*Malignancy (*if capsule is infiltrated*).

*Hepatic congestion.

*Cholestasis.

ii- Fever of unknown origin.

iii- Ø Ø Of Jaundice with leucocytosis

* Amoebic liver abscess. * Ascending cholangitis.

* Liptospiral infection

NB : Hepatic patient with **right** pleural effusion :

* Amoebic hepatitis .

* Ascites.

Hepatic patient with **left** pleural effusion ⇨ T.B.

Investigation:

1- Investigations to detect Amoeba: **4S** (*See amoebic dysentery*)

2- Liver function tests:

- Usually normal, *Amoebic hepatitis is a focal lesion*.

- **Alkaline phosphatase** : ↑↑

3- US & aspiration of abscess.

4- Blood picture: Leucocytosis.

5-Chest X-ray:

- Raised right copula of diaphragm.

- Pleural complications may be detected.

6- Therapeutic test : Metronidazole is given & response is detected.

Treatment:

I- Medical treatment:

1- **Antiameobic drugs**: (*see Amoebic dysentery*)

Metronidazole (Flagyl): 750mg t.d.s for 10 days + chloroquine (250mg twice daily) for 3 weeks + Iodoquinol (Entocid).

2- General care:

- Rest.
- Light nutrient diet.

3- Symptomatic treatment: analgesics & antipyretics.

4- Treatment of complications: Antibiotics for 2ry infections.

II- Aspiration: In cases not responding to medical treatment.

III- Surgical drainage: indicated in:

- Huge abscess.
- Multiple abscesses.
- Cases not responding to medical treatment & aspiration.

Hepatoma

(Hepatocellular carcinoma)

- It's highly malignant tumor, from the time of presentation → death within < 6 months.

Predisposing factors:

1- Age: Usually > 40 y.

2- Sex: ♂ > ♀ 3 times.

3- Hepatitis: HBV, HCV.

4- Cirrhosis: especially haemochromatosis.

5- Aflatoxins: mycotoxins secreted from saprophytic fungi on stored grains.

N.B: Contraceptive pills → adenoma not hepatoma.

Clinical picture: *(when do u suspect hepatoma in hepatic patient?)*

1- Rapid unexplained deterioration of his condition : encephalopathy, loss of weight.

2- Right hypochondrial pain or appearance of local swelling.

3- Resistant ascites.

4-***Paramalignant syndrome*** : (*non metastatic manifestations*)

- Endocrinal :

  Due to abnormal peptides secreted from the tumor which may be similar to hormones :

  - Insulin like peptide → hypoglycemia.
  - Parathormone hormone → ↑ Ca.
  - ACTH like peptide → Cushing's.

- CNS : Polyneuropathy , myopathy , myasthenia .
- Cutaneaues : acanthosis negricans , dermatomyositis.
- Cachexia , clubbing.

Investigation :

1- Hepatoma markers:

i - α fetoprotein: ↑↑ in 65% of cases. (> 2000 ng%)

ii- Corboxy prothrombin.

2- Hepatic scanning: CT, MRI, US.

3- Portal venography: portal vein thrombosis.

4- Hepatitis B &/or C markers: usually + ve.

5- Liver biopsy → diagnostic, but better avoided.

Treatment:

1-Medical: Systemic or local cytotoxic chemotherapy (adriamycin) "unsatisfactory"

2- Surgical resection : This is the treatment of choice for non-cirrhotic patients.

3-Hepatic embolization: injection of gel foam in blood supply of tumor.

4- Radiofrequency ablation.

5 -Hepatic transplantation.: the result is unsatisfactory.

Liver transplantation

A liver transplant is a surgical procedure to remove a diseased liver and replace it with a healthy liver from a donor.

Indications : 6

1. Liver cirrhosis of all causes with poor liver function e.g. Child-Pugh C, Hepatorenal syndrome, primary biliary cirrhosis.
2. FHF (Fluminant hepatic failure).
3. Budd- chiari syndrome.
4. Hepatocellular carcinoma.

5. Biliary atresia (*failure of bile duct formation*) : is the most common indication in children. ***MCQ***
6. Inherited disorders of metabolism :
    - Glycogen storage diseases.
    - Tyrosinemia.
    - α1-Antitrypsin deficiency.
    - Familial hypercholesterolemia.
    - Crigler-Najjar disease type I
    - Wilson's disease.
    - Hemochromatosis.

Contraindications :

I. Absolute :
    1. Severe systemic illness.
    2. Uncontrolled sepsis.
    3. Extrahepatic malignancy.
    4. Advanced cardiopulmonary disease.
    5. AIDS.

II. Relative :
    - Age > 70
    - Portal vein thrombosis.
    - Hepatoma more than 3cm in diameter.
    - Renal failure.
    - Severe obesity or malnutrition.
    - Uncontrolled psychiatric disorder.

Complications : 6

1. Liver graft rejection : acute or chronic rejection.
2. Hepatic artery thrombosis, biliary obstruction or leak.
3. Postoperative bleeding.
4. Postoperative infections, recurrent hepatitis.
5. Postoperative malignancy : lymphoma, hepatoma.
6. Renal dysfunction : Hypoperfusion injury, Drug nephrotoxicity.

Surgical technique :

1. **Orthotopic liver transplantation** :
   - The native liver is removed and the donor organ is inserted into the same location. In this case, the liver donor is someone who has recently died.
   - During the anhepatic phase, coagulopathy, hypoglycemia, hypocalcemia, and hypothermia must be managed by the anesthesiology team. Large volumes of blood and volume expanders may be required during surgery.
   - A typical transplant operation lasts 8 h, with a range of 6 to 18 h.
2. Auxiliary transplantation : The patient's liver is NOT entirely removed.
3. Split liver transplantation : The liver of the donor is split into 2 pieces to supply 2 patients.
4. **Living donor liver transplantation** (LDLT) : part of the liver (usually right lobe) of the patient's relative is transplanted.

Immunosuppressive drugs : Cyclosporine, Predinsone, Mycophenolate.

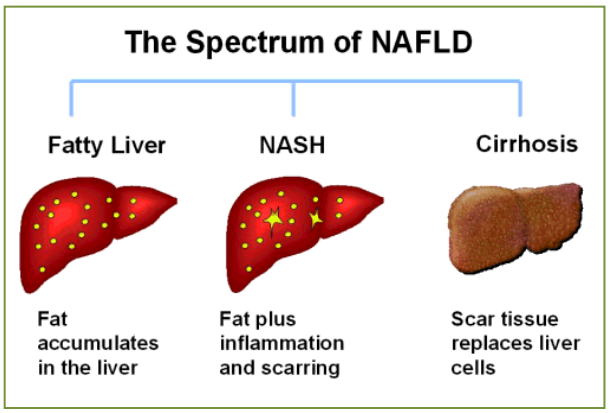
Liver donor requirements : The criteria for a liver donation include:

- Good health.
- Compatible blood group and organ size between donor and recipient.
- Having a charitable desire of donation without financial motivation.
- Being between 18 and 60 years old.
- Should be negative for HIV, HBV, and HCV.

Non Alcoholic Fatty Liver Diseases (NAFLD)

Definition :

- It is one cause of fatty liver in which there is a fat deposition in hepatocytes, not due to excessive alcohol use.
- It is becoming now one of the **most** common causes of chronic liver damage worldwide.
- **Steatosis** (*simple fatty liver*) : Fatty infiltration without inflammation.
- **Steatohepatitis** *(Non Alcoholic Steato-Hepatitis, NASH)* : Steatosis with inflammation that may lead to progressive fibrosis & cirrhosis.



Etiology :

a) Primary : Idiopathic.

b) Secondary :

- **Insulin resistance** associated with type II DM.
- **Obesity**.
- **Metabolic syndrome**.
- Hypertriglyceridemia.
- Malnutrition & rapid weight loss.
- Surgical : Gastric & jejonoileal bypass.
- Wilson's disease.
- Drugs & toxins :
  - ☠ **A**miodarone.
  - ☠ **A**spirin (rarely as part of Reye's syndrome in children).
  - ☠ **P**esticides.
  - ☠ **C**ortisone.
  - ☠ **C**hloroquine.
  - ☠ Methotrexate.

Pathogenesis :

- The pathogenesis of NAFLD is still *unclear*. Hepatic steatosis is due to lipid accumulation, mainly of triglycerides, within hepatocytes.
- Accumulation of hepatic fat is closely linked to insulin resistance, which increases lipolysis of peripheral adipose tissue with resultant increased fat influx into the liver in the form of free fatty acids.
- The injury may be due to direct cellular toxicity of excess free fatty acids, oxidant stress or lipid peroxidation.

Clinical picture :

- Usually asymptomatic.
- Pain, heaviness & discomfort in the right hypochondrium.
- Palpation : enlarged liver with a smooth surface & soft to firm consistency.

Investigations :

I. **L**ab :
   - Elevated ALT and AST.

   > *There is **no relation** between the degree of ALT elevation & the histological severity of steatosis or fibrosis.*

   - Bilirubin, albumin and prothrombin time are usually not affected in fatty liver disease until cirrhosis and liver failure develop.
   - Lipid profile : hypertriglyceridemia and/or elevated low-density lipoprotein (LDL)

II. **L**iver imaging : US, CT, MRI.

III. **Liver biopsy** is the *gold standard for diagnosis*. It is the only way to confirm the presence or absence of NASH.

Diagnosis of NAFLD/NASH :

- Involves history-taking to exclude significant alcohol intake.
- Involves the exclusion of other possible causes of abnormal liver tests e.g. absence of serological evidence of viral hepatitis.
- Consider **liver biopsy** for diagnostic and prognostic purposes.

Treatment :

1. Lifestyle modifications :
   - Exercise (30 minutes thrice weekly) and dietary modifications.
   - Reduce sedentary lifestyle.
   - Avoid too rapid weight loss (>1.6kg/week).

2. Pharmacologic therapy :
   - Insulin sensitizers : Thiazoladinediones, metformin.
   - Anti-oxidants : e.g. vit E to decrease the oxidant stress induced by accumulating lipid.
   - Ursodeoxycholic acid (UDCA) and lipid-lowering drugs.

3. Surgical therapy :
   - Bariatric surgery for patients with BMI >32.5kg/m^2 with co-morbidities or BMI >37.5 kg/m^2 without co-morbidities.
   - Liver transplantation in a patient with decompensated NASH cirrhosis.

Ascites

The word ascites is of Greek origin (askos) and means sac

Definition :

- Excessive accumulation of fluid in peritoneal cavity. Healthy men have little or no intraperitoneal fluid, but women may normally have as much as 20 ml depending on the phase of menstrual cycle.

Causes:

I. Transudative ascites :

a) **Increased hydrostatic pressure** : SAAG > 1.1

= Portal hypertension with its causes :

- **Liver cirrhosis : The most common cause.**
- **Supra-hepatic causes** :
  - RSHF, constrictive pericarditis, TI & TS
  - Budd- Chiari syndrome & IVC obstruction.
- Infra-hepatic causes : Portal vein thrombosis.

b) **Diminished osmotic pressure (Hypoalbuminemia) :**

- **End stage liver disease :** poor protein synthesis.
- **N**ephrotic syndrome.
- **N**utritional : severe malnutrition , malabsorption.

c) **M**iscellaneous:

- **M**eig's syndrome: (ovarian tumor, Ascites & pleural effusion)
- **M**yxedema : does not cause ascites directly. The ascites occurs because of myxedema related congestive heart failure.
- Chronic hemodialysis : occurs in fluid overloaded dialysis , most of patients also have cirrhosis.

II. Exudative ascites : ↑ permeability of peritoneal capillaries, SAAG < 1.1

- **P**eritoneal disease : TB peritonitis , SBP. - Mesothelioma.
- **P**ancreatitis.

III. Chylous ascites : Thoracic duct obstruction (by lymphoma).

Clinical picture:

Symptoms:

- **D**istension.
- **D**yspepsia.
- **D**yspnea.
- **D**evelopment of abdominal hernia.

Signs:

1- **Inspection:**

- **D**istension of the abdomen (mainly in flanks) ± visible vein.
- **D**ivercation of recti.
- **D**ownward shifted , everted umbilicus and may be umbilical hernia.
- **D**ilated veins on the abdominal wall :
    - Portal hypertension : Caput medusa.
    - IVC obstruction.

2- **Palpation:**

- Fluid thrill in tense ascites.
- Liver & spleen may be felt by dipping method in tense ascites.
- Abdominal masses may be felt : in TB & malignancy.

3- **Percussion:**

- Rounded central resonance with a peripheral " U " shaped dullness in the flanks down to the bed. The resonance over the umbilicus occurs in ascites because bowel floats on the top of abdominal fluid.
- **Shifting dullness** in moderate ascites (> 500 ml) : It is the most important clinical sign of ascites.
- Percussion in Knee elbow position in mild ascites (< 500 ml) : dullness around the umbilicus.

4- **Auscultation:**

- Venous hum may be heard over dilated vein.
- Puddle sign (auscultatory percussion) : *see clinical book*

Pleural effusion may occur secondary to ascites : due to passage of fluid through defects in the diaphragm.

Differential diagnosis : **F**'s (*causes of abdominal distension*)

i. **F**at (obesity) : sunken umbilicus , no shifting dullness.
ii. **F**luid (ascites) : flanks > centre (*frog abdomen*).
iii. **F**ull urinary bladder : umbilicus shifted upward , fullness is central.
iv. **F**latus (gaseous distension) : generalized hyper-resonance.
v. **F**etus (pregnancy) : needless to say in ♀ only . ☺

Investigations:

I. Investigations to detect the ascites :

Abdominal ultrasound & CT : detect ascites even in very small amount (30 ml) & also detect the cause e.g. liver cirrhosis.

II. Ascetic fluid analysis : *To detect the type of ascites*

- **Serum-Ascites Albumin Gradient (SAAG)** : see below
- Cell count :
  - An ascetic fluid with high RBCs suggests :
    - Malignancy.
    - TB.
    - Pancreatitis.
  - An ascetic fluid with high WBCs :
    - PMN > 250 /mm^3 ⇨ suggests SBP.
    - TB peritonitis : > 70% lymphocytes.

- Culture & sensitivity test : Ziehl Neelsen stain (ZN) for TB.
- Amylase to exclude pancreatic ascites.
- Cytology for malignant cells.

	Exudate	*Transudate*	
- Proteins	>	<	3 gm%
- Specific gravity	>	<	1016
- LDH	>	<	200 IU/L

III. Investigations for the cause :

- For liver cirrhosis : liver function tests , Ultrasound.
- For TB & malignancy : laparoscopy & biopsy.

Serum - Ascites Albumin Gradient (*SAAG*)

MCQ

- It is calculated by :

Serum Albumin - Ascitic fluid Albumin concentration

- **Clinical value :**
  - **SAAG ≥ 1.1** ⇨ *indicates that the ascites is due to portal hypertension regardless of its cause* e.g. Liver cirrhosis, Congestive heart failure, Budd-Chiari syndrome.
  - **SAAG ≤ 1.1** ⇨ Exudative ascites (*non portal hypertension etiology*) ***e.g.***
    - Infection : TB , SBP.
    - Cancer : 1ry or metastasis.
    - Pancreatitis.
    - Vasculitis.
    - Nephrotic syndrome.

Treatment: See before (6 items)

Refractory ascites :

- Ascites with lack of response to : 400 mg spironolactone plus 160 mg lasix daily with salt restricted diet for at least one week.
- Lack of response : Mean weight loss of less than 0.8 kg over 4 d and urinary sodium output less than the sodium intake.
- There are 2 types :
  1. Diuretic-resistant ascites : Lack of response to sodium restriction and diuretic treatment.
  2. Diuretic-intractable ascites : Development of diuretic-induced complications that prevent the use of an effective diuretic dosage.
- Diuretic-induced complications :
  - Hepatic encephalopathy.
  - Renal impairment.
  - Hyponatremia, Hypo- or hyperkalemia.
- Currently, serial large volume paracentesis (LVP), transjugular intrahepatic porto-systemic shunt (TIPS) & liver transplant are the mainstay treatment options.

Etiology	Treatment
Lack of salt resection	Treated by adequate salt restriction
Severe hypoalbuminemia	IV albumin.
Hyponatremia	Fluid restriction & IV manitol
Associated serious conditions : e.g. SBP (*spontaneous bacterial peritonitis*)	Treatment of the cause e.g. Cefotaxime: or Ciprofloxacin for 10 days.
Terminal case	• Le veen shunt : Peritoneo- venous shunt • TIPS. • Ascites ultrafiltration & reinfusion : Aspiration of ascetic fluid to concentrate it, then reinfusion to the patient IV. • Liver transplant.

Malignant ascites:

Etiology:

1- 2ry tumor : Stomach, liver, pancreas.

2- 1ry tumors : Mesothelioma (rare).

Clinical picture:

1- **M**assive rapidly accumulating ascites.

2- Abdominal **m**asses.

Aspiration of Ascitic fluid:

- Hemorrhagic. - **M**assive. - **M**alignant cells.

Premature ascites:

Ascites in cirrhotic patient before shrunken liver e.g.

- Bleeding.
- Hepatitis.
- TB peritonitis.

- Ascites without LL edema:

- Ascites precox e.g. pericardial effusion.
- Local peritoneal disease.
- Diuretic therapy (e.g. *lasix)* in cirrhotic ascites may cause relieve of LL edema with persistence of ascites.

Causes of Hepatomegaly:

1- **Infections**: Hepatitis, Bilhariziasis, Amoebiasis, Fascioliasis, TB.

2- **Inflammation**: Connective tissue disease & rheumatic disease.

3- **Infiltration**: Fatty liver, glycogen storage disease & amyloidosis.

4- **Malignancy**: 1ry & 2ry, Leukemia, Lymphoma.

5- **Congestive** liver.

6- **Cholestasis:** obstructive Jaundice particularly extra-hepatic.

- Mild enlargement: < 5cm from costal margin.
- Moderate enlargement → 5-8 cm from C. margin.
- Severe enlargement > 8cm below C. margin e.g. Leukemia, Lymphoma, Amyloidosis.

Drug induced liver diseases:

1- **Acute hepatitis**: Alcohol, **D**DT, **h**alothane, **p**aracetamol, **I**NH.

2- **Chronic hepatitis**: Alcohol, INH, methyldopa.

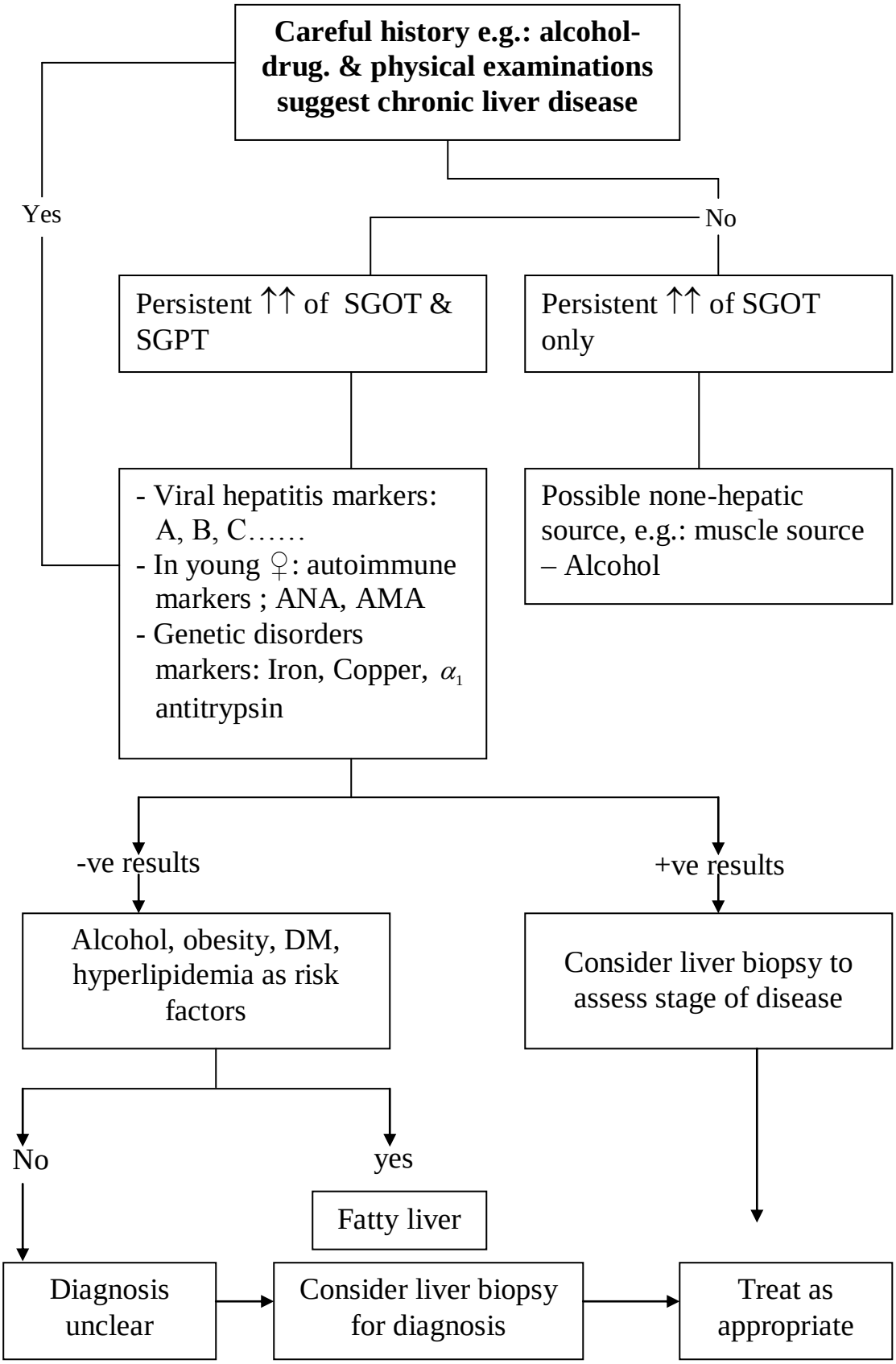
3- **Fatty Liver**: Alcohol, Amiodarone, tetracycline, valproic acid.

4- **Liver cirrhosis**: **M**ethyldopa, **I**NH, **m**ethotrexate.

5- **Cholestasis**: **A**nabolic steroid, **P**AS, **C**hlorpromazine, **D**indivan, **E**rythromycine.

Hepatic emergencies:	
-FHF	- Hepatic encephalopathy.
-Esophageal varices.	- Hepatorenal syndrome.
-Fever.	- Dyspnea due to ascites.

Approach to asymptomatic patient with elevated transamaineses :



Liver commentaries

The first case

The case start with either Bilharziasis (farmer) or hepatitis (blood transfusion)

⇩

Liver cirrhosis *why* ? ☞ LCF manifestations (Jaundice , ascites , ...)
☞ Portal hypertensions (Esoph. varices)

⇩

Complicated by : one of the following 5

Hepatoma	SBP	Hypersplenism	Encephalopathy	B.corpulmonale
- Rapid unexplained deterioration. - Resistant ascites. - Paramalignant syndrome.	- Aspiration of ascetic fluid : WBCs > 250/cm2 - Improved by antibiotics. - Resistant ascites. - Abdominal tenderness & fever.	-↓ WBCs,RBCs, platelets - Notice that portal hypertension is an important cause of hypersplenism.	- Precoma manifestations (2 SAD) - Coma.	- History of B. - pulmonary HTN. - RSHF

So,.. the final diagnosis is liver cirrhosis **complicated by** one of the 5's above.

The second case

Ameobic hepatitis :

A case of fever , right upper quadrant pain & tenderness , moderate hepatomegaly with or without jaundice , ↓ air entry on base of right lung (e.g. pleural effusion) . Also leucocytosis , ↑↑ alkaline phosphatase.

The third case

Wilson disease :

The family history, clinical examination & laboratory tests show the presence of acute liver failure, plus neurological manifestations e.g. abnormal movement. All point to the diagnosis of Wilson's disease.

The fourth case

Acute hepatitis

Jaundice, right upper quadrant pain, fatigue and markedly elevated ALT & AST make the diagnosis of acute hepatitis.

1- A 42 year old man presented because of increasing abdominal girth over the previous 2 weeks. His weight had increased only 3 pounds . He denied recent fever , chills, nausea , vomiting , melena , hematemesis or abdominal pain ,but did have a previous episode of esophageal variceal bleeding treated with sclerotherapy.

Physical examination :

Temp. 37C , pulse : 84b/m , Respiratory rate : 20/m , BP : 110/70 mmHg .

General : chronically ill appearing , Eyes : sclera icterus , skin : spider angiomata .

Abdomen : distension , venous redistribution pattern on the abdominal wall, tense ascites , bowel sounds present . Liver not palpable and splenic tip palpable . Edema lower limbs.

Lab finding : WBC 11.400/cmm , with 87% PMNs , Het 31% , platelets 85000/cmm, PT 11.5 seconds , Na 137mEq/L , K 5.2mEq/L , HCO_3 : 27 mEq/L , AST : 72 , ALT : 58 IU/L , Alkaline phosphatase : 18 KAU , Total serum bilirubin : 2.8 mg/dl , Paracentesis : ascites fluid is cloudy with WBC 1050/cmm , with 56% PMNs , ascites fluid protein 3 gm/dl . serum albumin 2.5 gm/dl . Medication including spirnolacton , frusemide , but a good response after addition of antibiotic.

a) **What is the professional diagnosis ?**
b) **Mention causes of hematemesis ?**
c) **What are causes of portal hypertension ?**
d) **What are the pathogenesis of the ascites in hepatic patient ?**
e) **In this patient, What is the most probable cause of ascites ?**
f) **What is the most suitable antibiotic used in treatment ?**

a) What is the professional diagnosis ?

Liver cirrhosis complicated by Spontaneous Bacterial Peritonitis (SBP).

- Cirrhotic patients with ascites and evidence of any clinical deterioration should undergo diagnostic paracentesis to exclude SBP.

- SBP occurs in 10% of cirrhotic patient due to loss of detoxification function of the liver. The key to the diagnosis of SBP is examination of the ascetic fluid : Neutrophils count > 250 cells / mm^3.

b) Mention causes of hematemesis ?

See GIT book

c) What are causes of portal hypertension ?

See GIT book

d) What are the pathogenesis of the ascites in hepatic patient ?

See GIT book

e) In this patient, What is the most probable cause of ascites ?

Spontaneous bacterial peritonitis

f) What is the most suitable antibiotic used in treatment ?

Cefotaxime: 2 gm t.d.s…IV or Ciprofloxacin 400 mg/12h for 5 - 10 days.

2- A 35 year old farmer , while working in the field , felt dizziness , fainting , extreme fatigability , nausea ,sweating and collapse . He was transferred to hospital where he passed black motion . On examination there was marked pallor , pulse 110/minute , BP : 90/60 mmHg . Abdominal examination revealed moderate enlargement of spleen. He was managed and discharged well in few days.

a) **Mention 5 data from the history that could help in reaching the diagnosis ?**
b) **Mention 5 added signs to clarify the diagnosis ?**
c) **What is the most probable diagnosis ?**
d) **Mention investigations that could be of help in assessing the case ?**
e) **How could you treat such case ?**

a) Mention 5 data from the history that could help in reaching the diagnosis ?

1- Farmer.
2- Splenomegaly.
3- Melena (black motion)
4- ↑ pulse.
5- History of drug intake , bleeding from other orifices , Dyspepsia.

b) Mention 5 added signs to clarify the diagnosis ?

1- Signs of portal hypertension : Splenomegaly, Caput medusa.
2- Signs of ascites : see GIT book P 70
3- Liver cirrhosis.
4- Spider naevi , palmer erythema , pallor , jaundice.
5- PR : to exclude hemorrhoids , fissure.
6- Signs of RV enlargement.

c) What is the most probable diagnosis ?

Complicated portal hypertension (Rupture esophageal varices)
DD :
- Causes of upper GIT bleeding : ……
- B polyposis.
- B corpulmonale : syncope

3- HCV antibody positive patient is concerned that he may transmit the virus to his wife or children. They are tested and are to be negative for HCV antibody. He is relieved but asks for advice to prevent infecting them.

a) **What do you advice him ?**

b) **Enumerate extra-hepatic manifestations of hepatitis C ?**

a)

- HCV is spread by parenteral contact with infected blood. In contrast to hepatitis B , sexual transmission of HCV is inefficient thus, it is NOT recommened that couples in long term relationship alter their sexual practices (e.g. use of condoms, etc ..)
- Hepatitis C is NOT spread by hugging, sneezing or sharing a drinking glass.
- Household members of persons infected with HCV should not share items that might be contaminated with small amount of blood , such as nail clippers .....

4- A 14 year old boy presented with yellowish discoloration of the sclera, he gave a history of tiredness and fatigue for the previous few weeks. His mother gave a family history of similar presentation few years ago in his older sister and she died few weeks later.

On examination : The boy was conscious & afebrile but jaundiced. Pulse 100/m, BP 110/70. Chest and heart were clinically free. Abdominal examination showed shifting dullness. Bilateral mild lower limb edema was present. There were abnormal movements involving both upper limbs.

Investigations : total bilirubin 3.5 mg/dL, direct bilirubin 2.8 mg/dL, albumin 3 g/dL, AST 556 U/L, ALT 678 U/L, INR 2.5

a) **What is the most likely diagnosis ?**
b) **What further investigations should be done ?**
c) **What is the treatment of this condition ?**

a) The most likely diagnosis is **Wilson's disease**. The family history, clinical examination & laboratory tests show the presence of acute liver failure , plus abnormal movement. All point to the diagnosis of Wilson's disease.

b) Further investigations :

- Serum ceruloplasmin (low) and urinary Cu excretion (should be elevated).
- Slit lamp examination of the cornea for the presence of Kayser Fleischer ring.
- Brain MRI.
- Liver biopsy.

c) Treatment :

- Cu chelation : D penicillamine.
- Supportive measures for acute liver failure.
- Liver transplantation.

5- A 32 year old male went for a pre-employment assessment. He had past history of blood transfusion once 10 years ago after a car accident. Examination revealed no clinically detectable abnormalities. Investigations ALT 120 U/L, AST 80 U/L , total bilirubin 1 mg/dL, Anti-HCV- Ab positive.

a) **What further investigations would you recommend ? And why ?**
b) **What are the drugs used in treatment of this condition ? What is the duration of treatment ?**
c) **What are the contraindications of treatment ?**

a) The investigations :

I. Lab :
- Serum albumin, PT, CBC to assess the presence of liver cirrhosis.
- PCR : Hepatitis C virus RNA to confirm the diagnosis. Anti HCV Ab by ELIZA is used only for screening.

II. Imaging :
- Abdominal US : to assess the presence or absence of cirrhosis, portal HTN, Size of spleen.

III. Liver biopsy is indicated to detect the chronic hepatitis activity and degree of fibrosis.

b)
- Combined ttt with pegylated interferon & ribavirin is used in the ttt of chronic HCV
- Dose , Precautions : see book
- Duration of ttt : for 12 months. Treatment should continue for longer period especially in a case of HCV genotype 4 (genotype in Egypt).

c)
- Decompensated cirrhosis is considered a contraindication.
- Renal failure is an absolutely contraindication for ribavirin.

6- A 17 year old male presented to the outpatient clinic with fever, anorexia, and vomiting. The condition started 4 days before, and was associated with right hypochondrial pain that was not related to meals. There was no change in bowel habits. He noticed tea colored urine for the last day . There were no previous medical illness or drug intake.

Examination revealed temp 38 C, pulse 120/m, normal BP. He was jaundiced. Abdominal examination revealed tenderness over the right hypochondrium, hepatomegaly 5 cm below the costal margin. There was no Splenomegaly or ascites.

Investigations : Serum ALT 2650 U/L, AST 2320 U/L, total bilirubin 5 mg/dL, indirect bilirubin 2.2 mg/dL.

a) **What would be the possible diagnosis ? And Why ?**

b) **What further tests would you recommend to confirm the diagnosis ?**

c) **What is the treatment ?**

a) The diagnosis is an acute hepatitis (most probably Hep A)

- Jaundice, right upper quadrant pain, fatigue and markedly elevated ALT & AST make the diagnosis of acute hepatitis.
- The age, the absence of drug history plus the typical symptoms and signs make the diagnosis of hepatitis A most appropriate.

b) Anti HAV Ab (IgM) should be recommended to confirm the diagnosis.

c) Treatment is conservative (bed rest & symptomatic ttt). The condition is benign, resolves gradually and NOT complicated by chronicity.